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Journal:	*American Journal of Gastroenterology*
Manuscript ID	AJG-15-1478.R1
Manuscript Type:	Original Contributions
Keywords:	Esophagus, Gastric, Epidemiology, Esophageal adenocarcinoma, Gastric cancer, Incidence, Negative correlation, Atrophic gastritis, Helicobacter pylori
Manuscript Section:	Esophagus

264pap - Version for AJG (22.10.15) (1330h)

Worldwide Inverse Association between Gastric Cancer and Esophageal Adenocarcinoma Suggesting a Common Environmental Factor Exerting Opposing Effects

Short Title:
Association of esophageal adenocarcinoma & gastric cancer

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Authors' contributions:

MHD: Design, analysis and intellectual input; **MA**: Analyses and intellectual input; **DHB**: Design and intellectual input; **JJG**: Intellectual input; **DRM**: intellectual input; **DF**: Design and intellectual input; **KELMcC**: Concept of idea and overall supervision.

This study was funded by an NHS Greater Glasgow Endowment Fund, UK

Text word count: 3,860. Tables & Figures: 7, References 36.

Supplement: Tables: 1, Figures: 4

Conflicts of interests: None to declare

Abbreviations:
EAC: Esophageal Adenocarcinoma; CGC: Cardia Gastric Cancer;
NCGC: Non-Cardia Gastric Cancer; TGC: Total Gastric Cancer;
WASR: World Age Standardised Incidence Rate;
AAPC: Average Annual Percentage Change.

ABSTRACT

Objectives: The incidence of esophageal adenocarcinoma (EAC) is increasing while adenocarcinoma of the stomach is decreasing. We have investigated whether the incidences of these two cancers and their time trends might be inversely related pointing to a common environmental factor exerting opposite effects on these cancers.

Methods: For cross-sectional analyses data were abstracted from "Cancer Incidence in Five Continents" (CI5) Volume X and GLOBOCAN 2012. Relevant ICD-10 codes were used to locate esophageal and gastric cancers anatomically, and ICD-O codes for the histological diagnosis of EAC. For longitudinal analyses age standardised rates (ASR) of EAC and total gastric cancer (TGC) were extracted from CI5C-Plus.

Results: Estimated (2012) ASRs were available for 51 countries and these showed significant negative correlations between EAC and both TGC (males: CC=-0.38, p=0.006, females: CC=-0.41, p=0.003) and non-cardia gastric cancer rates (males CC= -0.41, p=0.003 and females CC=-0.43, p=0.005). Annual incidence trends were analysed for 38 populations through 1989-2007 and showed significant decreases for TGC in 89% and increases for EAC in 66% of these, with no population showing a fall in the latter. Significant negative correlation between the incidence trends of the two cancers was observed in 28 of the 38 populations over the 19-50 years of available paired data. Super-imposition of the longitudinal and cross-sectional data indicated that populations with a current high incidence of EAC and low incidence of gastric cancer had previously resembled countries with a high incidence of gastric cancer and low incidence of EAC.

Conclusion: The negative association between gastric cancer and EAC in both current incidences and time trends is consistent with a common environmental factor predisposing to one and protecting from the other.

Key words: Esophageal adenocarcinoma, Gastric cancer, Incidence, Negative correlation, Epidemiology, Atrophic gastritis, *Helicobacter pylori*.

STUDY HIGHLIGHTS

WHAT IS CURRENT KNOWLEDGE

- The incidence of esophageal adenocarcinoma (EAC) is increasing rapidly in Western populations.
- The incidence of gastric cancer is decreasing throughout the world.

WHAT IS NEW HERE

- We have demonstrated an inverse relationship between the current incidences of those two cancers for countries throughout the world.
- We have demonstrated an inverse relationship between the incidence trends of the two cancers within individual cancer registries.
- Countries with a current high incidence of EAC and low incidence of gastric cancer previously resembled countries with a current low incidence of EAC and high incidence of gastric cancer.
- The inverse association between these two cancers is consistent with changes in the prevalence of a common environmental factor predisposing to one and protecting from the other.

INTRODUCTION

Over the past three decades, esophageal adenocarcinoma (EAC) has been one of the fastest increasing malignancies in many countries[1,2]. The cancer is thought to be the result of gastroesophageal reflux damaging the distal esophagus and causing columnar metaplasia often with intestinal phenotype. This Barrett's mucosa has an increased risk of progressing to dysplasia and adenocarcinoma.

The environmental factors causing the recent marked increase in incidence of EAC are unclear. Central obesity is associated with both reflux and EAC and the increasing prevalence of obesity is likely to explain some of the rise in incidence of EAC [(3,4)]. Smoking is another well-established risk factor for esophageal adenocarcinoma [5]. However, the prevalence of smoking has decreased over more than six decades in most Western countries and thus this cannot account for more recent increases in incidence of esophageal adenocarcinoma [6].

Another possible explanation is that *H.pylori* infection has been protecting against acid reflux, and thus EAC, and this is being lost by the falling incidence of the infection[7]. There is a well-established negative association between *H.pylori* infection and both gastroesophageal reflux and EAC.[8,9] This negative association between *H.pylori* and EAC is independent of the other risk factors of EAC including smoking and BMI[10]. A proposed mechanism for the protective effect of *H.pylori* is that the gastritis induced by it may cause atrophy and reduced acid secretory capacity of the gastric mucosa. As the acidity of the gastric juice is its main damaging component, reduction of this by *H.pylori* would protect against reflux-induced esophageal damage and associated adenocarcinoma[11].

H. pylori atrophic gastritis is the major risk factor for non-cardia gastric cancer (NGGC)[(12)]. If *H.pylori* infection does protect against EAC by inducing atrophy and reduced acid secretion, there should be a negative association between NCGC and EAC at a population level as the gastric mucosal changes predisposing to gastric cancer would be the same as those protecting from EAC.

Opposing incidence trends for EAC and NCGC have been reported in a study of the population of the East of England [13].

This study examined the relationship between the current incidences of the two cancers in different geographical regions of the world. In addition, we studied the relation between changes in incidence of the two cancers over time.

MATERIALS & METHODS

Cross-Sectional Studies

Based on data from Cancer Incidence in Five Continents Vol. X (CI5X) [14] and GLOBOCAN 2012 [15], age-specific and age-standardized (world population) incidence rates (WASR) were estimated for EAC and gastric cancer by topographical subsite (cardia and non-cardia) in 2012. This method has been described in more detail by Arnold et al.[16] and Colquhoun et al.[17] In brief, sex- and age-specific (<65; ≥65 years) proportions of EAC were computed for all countries included in CI5X except for those with no cases of EAC in one of four substrata (male, female; <65, ≥65 years) (N=51). Similarly, the proportions of cardia cancer (C16.0) and NCGC (C16.1-6) cases out of all gastric cancers with known topography (C16.0-6) were calculated for each country included in CI5X and stratified by sex and the same broad age groups, provided there were two or more cases of cardia cancer (CGC) and NCGC within each sex and age group stratification. Where there were multiple datasets (from different regional cancer registries within a country), cases and populations were pooled to obtain estimated national proportions. The histological types of esophageal cancer and the topographical classification of gastric cancers were defined according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3) presented in Cancer Incidence in Five Continents Vol. IX (CI5IX) [18,19]. For this analysis, the national or regional proportions of CGC/NCGC and EAC cases determined in the previous steps were applied to the 2012 gastric and EAC incidence estimates in GLOBOCAN 2012. Age-standardized incidence rates were computed using the world standard population (Table 1).

Longitudinal Studies

For the longitudinal study, WASR of EAC and total gastric cancer (TGC) were extracted from Cancer Incidence in Five Continents-Plus (CI5-plus) [1]. Cardia and non-cardia subsite data were not used because there were few longitudinal data for the specific subsite and also because there have been continuous changes in the subsite assignation practices for gastric cancer in histopathology laboratories. A total of 38 populations around the world were selected for this study based on **a**) availability of data of esophageal cancer recorded by histology, **b**) a time period of at least 19 years ending in 2007, **c**) if separate datasets were available for ethnic groups, at least one dataset per ethnic group was selected. The incidence (WASR) of EAC and TGC at the start year (different for each registry), year 1989 (earliest time common for all populations) and year 2007 (end year) were reported in Table 2, for men and women separately.

Statistical Analyses

For the cross-sectional study, Spearman's rho correlations were used to explore the relationship between WASR of the two cancers. In the longitudinal study, in addition to Spearman's rho correlations for pairwise correlation of EAC and TGC, time trends for individual registries, regression modelling was used to estimate the degree of incidence changes over time as described by Kim et al [20]. Briefly, using Joinpoint Programme version 4.1.0 (National Cancer Institute, USA) we analysed the time trend data for each cancer, in each registry, in men and women individually (38 x2 x2= 152 datasets). The programme fitted the simplest Joinpoint model that the data allowed. The models used the log of the WASR for calculating the average annual percent change (AAPC) in rates and their corresponding 95% confidence intervals. When any comparisons were made between different populations, the AAPC was always limited to the same 19 year period (1989-2007). When correlations were made between the change of cancer incidence between the two cancers within the same population, we present this in two different forms, firstly for the full

length of available longitudinal data for each population and secondly, limiting it to the same common observation period (1989-2007).

As EAC is much more common in men, we have focused mainly on results for men within the main text but have provided comparable analyses for women in the supplement.

RESULTS

A. Cross-sectional Study of National data

Incidence rate estimates were available for 51 countries (Table 1). There was a wide range in the rates of both gastric cancer and EAC across these different countries. The incidence of EAC varied from 0.23 per 100,000 person-years to 7.24. The incidence of TGC varied from 2.84 to 62.26 and that of NCGC from 1.75 to 58.64. In general terms, gastric cancer incidence was highest in East Asia and lowest in Western Europe and North America whereas EAC showed the opposite trend. In all 51 countries except the UK, EAC incidence rates were lower than the TGC rates and in 43 of 51 countries also lower than the NCGC incidence rate.

Statistically significant negative correlations between the incidence rates of EAC and both TGC {men (CC= -0.38, p=0.006), women (CC= -0.41, p=0.003)} and NCGC incidence {men (CC= -0.41, p=0.003) and women (CC= -0.43, p=0.005)} were observed.

The wide range in incidence of both EAC and TGC together with their inverse correlation resulted in a more than 200-fold range in the ratios of TGC to EAC across the different countries (more than 200:1 for the Republic of Korea to less than 1:1 for the UK)

Despite the strong negative correlation between the incidence rates of the two cancers, inspection of the data points indicated that in two respects the correlation was not linear (Fig. 1a.b). Firstly, the incidence of EAC seemed to be at a similar low level for all countries with moderate or high gastric cancer incidence and with a progressive rise in incidence at lower gastric cancer levels. The incidence of TGC below which the rise in EAC was apparent was approximately 15 per 100,000p/y in men (Fig. 1) and 7.5 per 100,000p/y in women (Fig. S1a,b). Secondly, when the incidence of TGC was low, the level of EAC incidence varied

considerably between countries with some showing marked elevation, some moderate and some no elevation. The equivalent figures for women showed a similar pattern though this was less clear due to much lower incidence rates (see Fig. S1a,b in supplement).

In order to investigate further the geographical distribution of the countries according to their TGC and EAC incidence rates, we sub-divided them into 4 groups (Fig. 1c). In men, the first 3 groups consisted of countries with low TGC incidence (<15 per 100,000 p/y) and EAC incidence high (>5) - Group A, medium (1.5-5) - Group B, and low (<1.5) – Group C. The fourth group (D) consisted of countries with high rates of gastric cancer (>15) and low EAC (<1.5).

The countries in these different groupings are shown in Figure 2. Group A with the highest rate of EAC and low (<15) TGC was limited to the UK, the Netherlands and Ireland. Group B with moderate EAC and low TGC (<15) comprised Northern America, Australia, New Zealand, Germany, Belgium, Denmark, Finland, Norway, France, Brazil and Uruguay. Area C with low EAC and low TGC (<15) was a very heterogeneous group from around the world (Thailand, Phiippines, India, Bulgaria, Croatia, Egypt, Israel, Italy, Spain, Poland, Serbia, Slovakia, Singapore); Group D with low EAC and moderate to high TGC includes South American countries, Eastern Europe, Korea, China, Japan, Russia, Iran and Turkey.

In women, sub-dividing all countries into groups based on their rates of esophageal and gastric cancer incidence demonstrated similar geographical patterns (Fig S2 in supplement).

B. Longitudinal Study

B1. Changes in incidence of esophageal adenocarcinoma and gastric cancer

To explore the rate of change in incidence of EAC and TGC during the period of 1989-2007 in males, we calculated average annual percentage change (AAPC) for each of the 38 populations individually, and presented these in Fig. 3, ordered by the most recent incidence of EAC. During this time period, most populations (34/38, 89%) had experienced a significant decrease in the incidence of TGC, with these 34 showing a range of AAPC from -

1.4% (95% CI: -2.1, -0.6 in Japan, Miyagi) to -5.1% (95% CI: -5.8, -4.3) in Austria, Tyrol. Twenty-five of 38 (66**%**) populations showed a significant increase in incidence of EAC during the period of observation and no population showed a significant fall in incidence (Fig. 3). Annual increases in EAC incidence ranged from 1.5% (95% CI: 0.8, 2.3 in Victoria, Australia) to 11.7% (95% CI: 3.7, 20.2 in Estonia).

We investigated any differences between the 13 populations showing no significant rise in EAC and the 25 population showing a rise. The populations which showed no significant change in EAC showed a rate of decrease in TGC (AAPC range -4.9% to 0.7%) similar to those that showed increase in EAC (AAPC range = -5.1% to -1.4%), (p=0.504). Likewise, the registries showing no rise in EAC did not differ from those showing an increase in that the two groups had a similar most recent (2007) TGC incidence (9.5 vs 9.6/1000,000py; p=0.584).

The data for women again showed a similar pattern and are shown in Fig S3. Additionally, further analyses using longer but varying periods of observation (19-50 years) were conducted with similar findings and are presented in the supplement as Fig S4 for men only.

B2. Correlation of Incidence trends of EAC and TGC

We looked for any correlation between the incidence trends for both cancers for those 38 populations with sufficient longitudinal data and included the full observation period of paired data (ie not limited to 1989-2007) (Table 3). In men, significant negative correlations between incidence rate trends of EAC and TGC over time were present in 27 of the 38 populations when compared over preceding 19-50 years and evaluated in pairs (Table 3). Positive correlations were not observed for any population.

When the calculation of correlations between EAC and TGC incidence trends was limited to the common but shorter observation period (last 19 years of 1989-2007), the magnitude of correlations was weaker in some of the populations. Only 19 of 38 populations showed

significant negative correlations for men and 7 of 38 for women (see Table S2 in supplement).

C. Relationship of longitudinal and cross-sectional data

We investigated the relationship between the cross-sectional data of most recent incidences of the two cancers and the longitudinal incidence trends. On the cross-sectional scatter plot figure showing the correlation between current incidence of EAC and TGC across different countries we superimposed a line indicating the incidence trend over preceding years available from the longitudinal data. This allowed us to examine the changes in incidence of both TGC and EAC cancer over time and how it related to their current incidences in different countries. To facilitate visual inspection we did this separately for each of the four categories of countries i.e. groups A,B,C and D based on incidence pattern of the two cancers (Fig. 4). For the longitudinal data we selected the 3 populations from each of groups A, B, C and D with the longest observation periods.

The resulting plots indicated that the countries with current low incidence of TGC and current high, medium or low incidence of EAC had previously resembled countries with a current high incidence of TGC and current low incidence of EAC. As the incidence of TGC has fallen this has been accompanied by varying degrees of increase in EAC with some populations showing a marked increase, some moderate increase and some no increase.

DISCUSSION

Our study has demonstrated an inverse association between the incidence of EAC and gastric cancer. This is apparent with respect to both the current incidences of these two cancers across different countries and with respect to changing incidence of the two cancers within the same populations over time. The inverse association is intriguing in view of the fact that the two cancers are biologically very similar. Both EAC and TGC arise from epithelia of closely adjacent, indeed abutting regions of the upper gastrointestinal tract, both

are the result of chronic damage and inflammation exerted by their luminal environment and both usually show very similar and often indistinguishable histological appearance.

Our cross-sectional study showed that both cancers were similar in having a wide range in current incidence rates (20-30 fold in males) across the different countries but different in having contrasting geographical patterns. The longitudinal studies showed that the incidences of both TGC and EAC had changed markedly over recent decades but these changes were in opposite directions and there was a statistically significant inverse association between the changing incidence rates of the two cancers in 71% of the registries.

Combining the cross-sectional and longitudinal data provided an overall picture of what has been happening to these two cancers over time and in different regions of the world. Previously, most countries had a high incidence of gastric cancer and a low incidence of EAC. Since then, the incidence of gastric cancer has fallen in all countries and as it has reached low levels it has been accompanied by varying degrees of increase in EAC with some regions showing marked increase, some moderate and others no increase.

What is the explanation for the opposing incidences and time trends of these two cancers? Could differences between countries in classification of junctional cancers into esophageal versus gastric locations and/or changes in classification of these cancers over time explain some of the observations? In the cross-sectional study, we found that the inverse association remained strong and indeed became slightly stronger by excluding cancers occurring at the gastric cardia and thus more likely to be misclassified. The longitudinal data only provided information on TGC. Spurious inverse association between incidence trends of the two cancers due to changing classification of cardia junctional cancers would only be likely to be a significant issue in countries with a very high incidence of gastric cancer and low incidence of EAC as misclassification of a small proportion of the former could substantially increase the latter[21]. Such misclassification, however, could not explain the strong inverse incidence trends as they were most apparent in countries with lower gastric cancer incidence [22].

The marked changes in incidence of TGC and EAC over a short time scale indicate the influence of a changing environmental factor. In addition, the inverse association between the changing incidences indicates that the environment factor is exerting opposite effects on these two cancers. The environmental factors which are thought to explain the falling incidence of TGC include a falling incidence of *H. pylori* atrophic gastritis, dietary changes and reduced smoking [23,24]. Could the falling incidence of any of these be associated with an increase in EAC and thus explain the inverse association in the incidence trends of the two cancers? Smoking is not a candidate as it is a similar risk factor for both cancers [5,25]. Dietary changes might be important. There is some evidence that increased intake of vitamins and reduced salt consumption may have contributed to the falling incidence of gastric cancer [26,27]. These specific dietary factors would not in themselves explain the increase in EAC and indeed increased vitamin consumption may protect from EAC [28]. However, increased caloric intake and associated obesity is a well-established risk factor for EAC [28]. It is therefore possible that changes in the diet comprising both a fall in salt content and increased caloric content could produce a fall in total TGC and rise in EAC. However, a recent analysis indicated that increasing obesity may only account for 6.5% of the increase in incidence of EAC and suggesting the role of additional environmental factors [3].

Another environmental factor which might exert opposite effects on the incidence of the two cancers is *H. pylori* atrophic gastritis which is the most important etiological factor for NCGC [29]. In countries with a high incidence of gastric cancer there is also a high incidence of atrophic gastritis and associated impaired gastric acid secretion [30]. In contrast, in subjects without *H.pylori,* gastric acid is maintained and shows no decline with increasing age[31]. In countries with a high incidence of gastric cancer the high prevalence of *H.pylori* atrophic gastritis will protect from EAC as any gastroesophageal refluxate will have reduced ability to damage the esophagus due to its reduced acidity. Epidemiological studies have shown consistent associations between *H. pylori* and both TGC and EAC being positive with respect to the former and negative with respect to the latter [10]. As the prevalence of *H.pylori* atrophic gastritis falls, it will be accompanied by a fall in gastric cancer but

potentially also a rise in EAC due to increasing gastric acidity. The prevalence of *H. pylori* infection has fallen over recent decades in association with improved living conditions [32].

Interactions between *H. pylori* and dietary factors might also be important. There is some evidence that a high vitamin, low salt diet may protect from the development of atrophic gastritis in *H. pylori* infected subjects [33]. Improved living conditions, with accompanying fall in *H. pylori* prevalence as well as increased vitamin and reduced salt intake could together markedly reduce atrophic gastritis with resultant fall in TGC and increase in EAC.

In the previous study by Anderson et al showing a strong negative association between *H.pylori* and esophageal adenocarcinoma, the association persisted even after correcting for atrophic gastritis detected by serum pepsinogens [8]. However, it is recognised that serum pepsinogens are insensitive markers of atrophy[34]. In addition, *H.pylori* body-predominant gastritis is associated with reduced gastric acid secretion independent of atrophy.[35] Furthermore, body-predominant gastritis is an important risk factor for gastric cancer[36] so even without significant atrophy it might both promote gastric cancer and protect from esophageal adenocarcinoma.

Though there were strong inverse associations between the two cancers with respect to both current incidences and time trends, there was a group of countries with a low incidence of both cancers. This was a heterogeneous group consisting of Thailand, Philippines, Singapore, India, Egypt, Israel, Bulgaria, Croatia, Italy, Spain, Poland, Serbia and Slovenia. Due to the limited availability of longitudinal data for many of these populations, it was difficult to determine whether their low incidence of both cancers was due to the absence of a rise in EAC as their incidence of TGC fell, or whether they had never had a high incidence of TGC and were somehow protected from both cancers. It is possible that genetic and/or environmental factors present in some of these populations might inhibit the progression from inflammation to neoplasia which is a common final step in the pathways leading to both TGC and EAC. A lack of increase in EAC despite TGC falling to a low level might be due to genetic and/or environmental factors protecting from gastroesophageal reflux which is an

essential early step in the pathway to EAC. Comparative studies of countries with low versus high incidence of EAC despite low incidence of TGC may shed new light on the etiology and pathogenesis of EAC.

An important question is whether countries where gastric cancer incidence is still high but falling such as Japan and South East Asia will encounter a rise in EAC similar to that recently experienced in Western countries. A fall in the incidence of gastric cancer to a low level is not necessarily accompanied by a rise in esophageal adenocarcinoma as highlighted above. However, the current incidence of gastric cancer in Japan and South East Asia is still at a level which when present in Western countries was not yet associated with any rise in EAC and it will be interesting to observe what happens when this point is reached.

Strengths of our study include the use of high quality global surveillance data. Limitations also need however to be recognised. Incidence rates used in the cross-sectional analysis were based on country-, age- and sex-specific proportions of EAC from CI5X, which were then applied to GLOBOCAN 2012 data. Hence, they represent estimates of the true incidence rates within each country and should be interpreted with caution. Our inclusion criteria for the cross-sectional study furthermore resulted in a selection of 51 mostly high-income countries, which may not be fully representative on the global level. Pathological practices and classifications of histological subtypes have changed over time, which should be kept in mind when interpreting the results, especially from the longitudinal analyses. Also, registries covering different time periods (19 to 50 years) were included in some of the longitudinal analysis, making them not directly comparable. Finally, most of the countries included in the cross-sectional studies have more than one original cancer registry and even though we selected the largest registry available from each country, it may not represent the full national picture.

In conclusion, this study demonstrates a strong inverse association between gastric cancer and EAC with respect to both their current incidences and time trends, suggesting a changing common environmental influence exerting opposite effects on these two cancers. Though ecological studies do not establish causality, one biologically plausible

environmental factor which could explain this unusual inverse association is *H. pylori* atrophic gastritis. However, changes in disease incidence are usually the result of several interacting environmental factors and changes in lifestyle predisposing to obesity as well as dietary interactions with *H. pylori* to induce atrophy are also likely to be important.

FIGURE LEGENDS

Fig 1: Correlations between incidence rates (WASR) of EAC and gastric cancer in cross-sectional study in men.
Note: Each dot represents a dataset from a country, 1a: EAC versus total gastric cancer, 1b. EAC versus non-cardia gastric cancers, 1c: visual clustering of countries divided into groups A-D.

Fig 2: Maps of countries colour-coded with visual clustering of populations with different combinations of EAC and gastric cancer in cross-sectional study in men.
Note: For each country, a pooled national data has been used to create colour codes. The grey code indicates no data available. **A:** TGC<15 & EAC≥5, **B:** TGC<15 & 1.5≤EAC<5, **C**: TGC<15 & EAC<1.5, **D:** TGC≥15 & EAC<1.5.

Fig 3: Average Annual Percentage Changes (95% CI) of EAC versus TGC in men during short common period (1989-2007) of registration in populations.

Fig 4: Longitudinal data superimposed on cross-sectional cancer incidence by groups A-D in men.
Incidence of esophageal adenocarcinoma is shown on Y axis (per 100,000py) and incidence of total gastric cancer on X axis. The cross-sectional data of the most recent cancer incidence for different countries is shown by dots. For the three populations with the longest available longitudinal data, we have superimposed on the dot diagram a line indicating their incidence trend from start to end of registration period dates. The dates of the start and end of the incidence trend line is given above in box and the time-line is always from right to left.

Supplementary figures

Fig S1: Correlations between incidence rates (WASR) of EAC and gastric cancer in cross-sectional study in women.
Note: each dot represents a dataset from a country, 1a: EAC versus total gastric cancer, 1b. EAC versus non-cardia and other gastric cancers, 1c: visual clustering of countries divided into groups A-D.

Fig S2: Maps of countries colour-coded with visual clustering of populations with different combinations of EAC and gastric cancer in cross-sectional study in females.
Note: For each country, a pooled national data has been used to create colour codes. The grey code indicates no data available. **A:** TGC<7.5 & EAC≥1, **B:** TGC<7.5 & 0.3≤EAC<1, **C**: TGC<7.5 & EAC<0.3, **D:** TGC≥7.5 & EAC<0.3.

Fig S3: Average Annual Percentage Changes (AAPC) of EAC versus TGC in women during short common period (1989-2007) of registration.

Fig S4: Average Annual Percentage Changes (AAPC) of EAC versus TGC in men during full period (19-50 years) of registration.

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Table 1: Estimated age-standardised incidence rates (world) of gastric cancer and esophageal adenocarcinoma in different countries in cross-sectional study. The countries are listed based on incidence of Esophageal adenocarcinoma.

	Men					Women			
Country	**TGC**	**Cardia**	**NCGC**	**EAC**		**TGC**	**Cardia**	**NCGC**	**EAC**
United Kingdom	6.44	3.89	2.55	7.24		3.15	1.46	1.69	1.36
The Netherlands	7.61	3.39	4.22	7.05		3.9	1.03	2.86	1.19
Ireland	8.83	3.64	5.19	5.36		4.42	1.42	3	1.01
New Zealand	6.69	3.27	3.42	3.96		3.83	0.88	2.94	0.56
United States of America	5.33	2.6	2.73	3.62		2.7	0.66	2.04	0.42
Belgium	8.04	4.96	3.08	3.53		3.83	1.36	2.48	0.57
Australia	6.72	3.44	3.27	3.41		3.14	0.99	2.15	0.49
Denmark	8.32	5.79	2.53	3.07		3.05	1.27	1.78	0.76
Canada	6.95	3.26	3.69	2.99		3.12	0.83	2.29	0.42
Switzerland	5.01	2.21	2.8	2.59		3.58	0.89	2.69	0.49
Norway	5.61	2.41	3.2	2.32		3.82	0.91	2.91	0.43
Malta	11.08	6.1	4.98	2.3		5.53	1.2	4.33	0.11
Germany	10.66	3.84	6.82	2.16		5.44	1.01	4.43	0.28
Czech Republic	10.21	2.81	7.41	2.16		5.27	0.75	4.52	0.29
Uruguay	14.36	7.61	6.75	2.07		6.7	2.06	4.64	0.61
Argentina	9.87	2.79	7.08	1.98		4.19	0.71	3.48	0.44
Austria	9.2	4.89	4.31	1.97		4.83	1.42	3.41	0.23
Brazil	13.08	4.26	8.82	1.96		5.96	1.16	4.8	0.59
Finland	6.72	4.86	1.86	1.8		3.94	2.06	1.88	0.3
France (metropolitan)	6.97	3.03	3.94	1.56		2.8	0.48	2.32	0.33
Spain	10.97	2.91	8.05	1.27		5.11	0.66	4.45	0.18
Colombia	18.89	6.93	11.95	1.11		8.97	2.18	6.8	0.21
Lithuania	22.73	2.99	19.75	1.09		8.02	0.61	7.41	0.15
Turkey	17.92	4.49	13.43	1.09		10.93	2.34	8.59	0.21
Israel	9.71	4.03	5.68	0.94		4.9	1.45	3.45	0.2
Puerto Rico	5.28	1.37	3.91	0.94		3.11	0.48	2.64	0.26
Ukraine	22.39	4.36	18.03	0.9		9.14	1.29	7.85	0.16
Latvia	23.05	4.97	18.08	0.86		8.68	0.93	7.74	0.18
Bulgaria	14.51	2.71	11.8	0.86		6.99	0.88	6.12	0.12
Croatia	14.47	7.5	6.97	0.85		6.27	2.39	3.88	0.12
Iran, Islamic Republic of	20.6	13.37	7.22	0.85		9.72	5.4	4.32	0.85
Belarus	29.14	3.37	25.77	0.84		12.22	0.95	11.27	0.1
China	32.77	11.97	20.8	0.83		13.1	3.37	9.73	0.26
Russian Federation	24.45	4.74	19.71	0.79		10.8	1.58	9.21	0.13
Slovakia	13.95	3.43	10.52	0.79		6.58	0.92	5.66	0.15
Costa Rica	21.43	4.65	16.78	0.75		13.66	1.48	12.18	0.15
Chile	23.29	7.35	15.94	0.74		9.19	1.99	7.2	0.26
Slovenia	15.37	5.01	10.36	0.65		6.42	1.02	5.4	0.1
Italy	10.89	2.43	8.46	0.61		5.92	0.63	5.29	0.09
Serbia	11.94	6.69	5.25	0.59		5.68	2.94	2.75	0.14
Philippines	4.81	2.03	2.78	0.56		2.88	0.89	1.99	0.14
Egypt	2.84	1.09	1.75	0.52		2.27	0.55	1.72	0.28
Poland	13.19	7.87	5.32	0.5		4.95	2.08	2.86	0.09
Estonia	19.5	2.96	16.54	0.44		10.31	1.03	9.28	0.07
India	8.56	3.26	5.3	0.43		3.68	1.41	2.27	0.13
Japan	45.75	4.73	41.01	0.42		16.46	1.25	15.21	0.07
Saudi Arabia	3.84	1.36	2.48	0.42		2.41	0.72	1.69	0.15
Singapore	10.85	3.18	7.67	0.34		5.83	1.31	4.52	0.07
Ecuador	20.69	3.5	17.19	0.33		13.43	0.95	12.48	0.21
Thailand	3.77	1.36	2.41	0.27		2.49	0.8	1.68	0.08
Korea, Republic of	62.26	3.62	58.64	0.23		24.67	1.07	23.6	0.04

Table 2: List of recruited registries in longitudinal study, and incidence rates (WASR) of total gastric cancer and esophageal adenocarcinoma at the start, year 1989 and end of period

Study Population	Full-range Period (yrs)	Men						Women					
		EAC (start)	EAC (1989)	EAC (2007)	TGC (start)	TGC (1989)	TGC (2007)	EAC (start)	EAC (1989)	EAC (2007)	TGC (start)	TGC (1989)	TGC (2007)
Brazil, Goiania	1988 -2007 (20)	0.45	0.45	0.51	25.46	25.46	25.86	0.01	0.06	0.06	52.05	30.70	17.26
Estonia, all	1968 -2007 (40)	0.04	0.09	0.56	57.27	35.25	23.29	0.16	0.03	0.06	8.62	6.67	4.30
Thailand, Chiang Mai	1983 -2007 (25)	0.00	0.06	0.11	8.25	8.09	6.84	0.08	0.05	0.02	5.10	4.08	2.58
Switzerland, St Gall-Appenzell	1983 -2007 (25)	0.93	0.76	3.22	12.09	12.23	6.41	0.32	0.35	0.53	6.14	5.32	3.92
Israel, Jews	1963 -2007 (45)	0.06	0.08	0.86	24.84	13.26	9.58	0.00	0.05	0.17	8.63	7.96	7.01
Croatia, all	1988 -2007 (20)	0.26	0.26	0.63	28.98	28.98	17.36	0.02	0.04	0.09	19.41	10.89	7.19
Spain, Murcia	1983 -2007 (25)	0.74	1.21	1.44	17.88	15.67	10.46	0.09	0.02	0.24	5.96	5.02	3.31
Austria, Tyrol	1988 -2007 (20)	0.42	0.42	0.79	28.24	28.24	11.24	0.04	0.09	0.16	6.69	6.22	4.78
France, Bas-Rhin	1975 -2007 (33)	0.88	0.83	2.12	17.58	12.78	8.42	0.00	0.11	0.35	8.14	7.27	4.33
Spain, Granada	1985 -2007 (23)	0.58	0.39	1.16	17.77	14.92	10.02	0.03	0.03	0.22	16.40	16.40	6.93
Netherlands, all	1989 -2007 (19)	2.26	2.26	5.42	15.68	15.68	8.88	0.58	0.58	0.93	6.11	6.11	3.98
USA, Michigan, Detroit, Whites	1973 -2007 (35)	0.67	1.74	4.39	10.13	9.56	6.42	0.10	0.22	0.64	4.49	3.76	2.93
Switzerland, Vaud	1988 -2007 (20)	1.48	1.48	2.47	10.63	10.63	7.22	0.13	0.13	0.36	11.3	4.88	3.22
USA, Michigan, Detroit, Blacks	1973 -2007 (35)	0.30	0.48	1.03	16.24	16.10	12.08	0.04	0.05	0.19	14.78	6.19	5.20
Canada, Manitoba	1958 -2007 (50)	0.08	1.28	2.64	25.6	12.60	8.33	0.05	0.26	0.42	4.45	3.28	2.26
England, North West	1979 -2007 (29)	1.58	3.70	7.07	22.32	17.76	10.12	0.46	0.86	1.34	10.01	7.74	4.08
USA, SEER (9 Regs), Whites	1975 -2007 (33)	0.61	1.83	3.74	9.31	8.04	5.55	0.22	0.27	0.60	7.02	5.09	3.35
Scotland, all	1975 -2007 (33)	2.36	3.42	7.47	21.17	18.56	9.72	0.83	1.05	1.49	10.64	7.90	4.57
Australia, New South Wales	1983 -2007 (25)	0.71	1.54	2.67	12.36	10.82	7.54	0.00	0.26	0.50	8.03	6.46	3.68
Canada, Saskatchewan	1968 -2007 (40)	0.13	1.20	1.99	14.2	8.51	5.93	0.00	0.00	0.31	18.15	19.07	13.53
USA, Calif, Los Angel, Non-His Whites	1973 -2007 (35)	0.35	1.61	2.77	9.92	7.99	5.52	0.10	0.22	0.51	4.03	3.19	2.43
Japan, Osaka	1963 -2007 (45)	0.00	0.22	0.41	107.06	70.42	44.19	0.15	0.25	0.03	23.39	17.19	14.11
England, South & West	1979 -2007 (29)	1.40	3.46	5.84	17.21	14.79	7.02	0.30	0.48	1.11	6.99	3.77	2.72
Japan, Miyagi	1978 -2007 (30)	0.68	0.43	0.69	82.51	84.41	65.72	0.05	0.19	0.10	8.44	7.09	5.20
Slovakia, all	1973 -2007 (35)	0.15	0.35	0.78	42.30	25.06	16.43	0.00	0.04	0.15	8.29	5.40	3.80
India, Mumbai	1978 -2007 (30)	0.29	0.04	0.08	7.11	6.68	4.46	0.11	0.11	0.00	12.46	12.46	12.27
USA, SEER (9 Regs), Blacks	1975 -2007 (33)	0.17	0.46	0.74	15.30	15.04	10.43	0.00	0.00	0.14	23.97	23.97	10.48
Australia. Victoria	1983 -2007 (25)	1.23	1.74	2.64	14.84	12.33	7.97	0.12	0.20	0.45	5.27	4.40	3.47
Colombia, Cali	1983 -2007 (25)	0.19	0.68	0.87	32.46	33.40	25.82	0.00	0.07	0.18	7.82	6.31	4.81
Italy, Romagna	1988 -2007 (20)	0.44	0.44	0.45	41.78	41.78	20.34	0.23	0.05	0.03	38.26	34.52	22.21
Singapore, Chinese	1968 -2007 (40)	0.00	0.28	0.38	45.07	33.48	14.90	0.00	0.00	0.03	4.48	4.79	4.17
Denmark, all	1978 -2007 (30)	0.81	1.76	2.54	15.05	10.29	7.68	0.19	0.19	0.40	3.88	3.88	3.86
Philippines, Manila	1983 -2007 (25)	0.32	0.34	0.45	14.16	11.72	6.91	0.00	0.02	0.04	17.21	15.12	7.86
Italy, Torino	1985 -2007 (23)	0.41	0.55	0.82	20.25	19.18	10.65	0.00	0.00	0.16	8.94	9.15	5.40
Costa Rica, all	1980 -2007 (28)	0.55	0.52	0.63	48.40	39.53	24.65	0.08	0.08	0.08	11.87	11.87	7.22
USA, Calif, Los Angel, Blacks	1973 -2007 (35)	0.37	0.68	0.59	15.53	13.76	8.66	0.00	0.05	0.08	26.73	16.45	11.43
France, Isere	1979 -2007 (29)	0.33	1.98	1.51	13.26	14.81	7.36	0.04	0.05	0.28	6.81	3.54	3.01
USA, Calif, Los Angel, His Whites	1973 -2007 (35)	0.04	1.47	1.47	14.98	13.43	9.53	0.09	0.14	0.27	7.68	5.77	5.62

Table 3: Correlations between incidence (WASR) trends of esophageal adenocarcinoma and total gastric cancer In men in the two time periods- full range and 1989-2007.

Study Population	Population	Full Range				1989 - 2007	
	(2007)	Period (yrs)	CC	*P* value		CC	*P* value
Brazil, Goiania	588132	1988 -2007 (20)	0.048	0.84		0.098	0.70
Estonia, all	617828	1968 -2007 (40)	-0.420	**0.01**		-0.471	**0.04**
Thailand, Chiang Mai	741784	1983 -2007 (25)	-0.281	0.17		-0.109	0.66
Switzerland, St Gall-Appenzell	263298	1983 -2007 (25)	-0.590	**0.00**		-0.519	**0.02**
Israel, Jews	2674800	1963 -2007 (45)	-0.637	**0.00**		-0.173	0.48
Croatia, all	2137984	1988 -2007 (20)	-0.737	**0.00**		-0.713	**0.00**
Spain, Murcia	714667	1983 -2007 (25)	-0.394	0.05		-0.382	0.11
Austria, Tyrol	342794	1988 -2007 (20)	-0.530	**0.02**		-0.475	**0.04**
France, Bas-Rhin	534515	1975 -2007 (33)	-0.536	**0.00**		-0.458	**<0.05**
Spain, Granada	438332	1985 -2007 (23)	-0.442	**0.04**		-0.396	0.09
Netherlands, all	8100293	1989 -2007 (19)	-0.961	**0.00**		-0.971	**0.00**
USA, Michigan, Detroit, Whites	1390555	1973 -2007 (35)	-0.921	**0.00**		-0.821	**0.00**
Switzerland, Vaud	323759	1988 -2007 (20)	-0.402	0.08		-0.370	0.12
USA, Michigan, Detroit, Blacks	475552	1973 -2007 (35)	-0.271	0.12		0.193	0.43
Canada, Manitoba	588875	1958 -2007 (50)	-0.777	**0.00**		-0.402	0.09
England, North West	3223560	1979 -2007 (29)	-0.926	**0.00**		-0.800	**0.00**
USA, SEER (9 Regs), Whites	10682176	1975 -2007 (33)	-0.972	**0.00**		-0.834	**0.00**
Scotland, all	2485606	1975 -2007 (33)	-0.961	**0.00**		-0.913	**0.00**
Australia, New South Wales	3420484	1983 -2007 (25)	-0.888	**0.00**		-0.810	**0.00**
Canada, Saskatchewan	495639	1968 -2007 (40)	-0.724	**0.00**		-0.083	0.73
USA, Calif, Los Angel, Non-His Whites	1446148	1973 -2007 (35)	-0.843	**0.00**		-0.520	**0.02**
Japan, Osaka	4366616	1963 -2007 (45)	-0.915	**0.00**		-0.572	**0.01**
England, South & West	3442830	1979 -2007 (29)	-0.924	**0.00**		-0.774	**0.00**
Japan, Miyagi	1140676	1978 -2007 (30)	-0.383	**0.04**		-0.574	**0.01**
Slovakia, all	2621095	1973 -2007 (35)	-0.818	**0.00**		-0.463	**<0.05**
India, Mumbai	7479777	1978 -2007 (30)	-0.425	**0.02**		-0.567	**0.01**
USA, SEER (9 Regs), Blacks	1724091	1975 -2007 (33)	-0.592	**0.00**		-0.434	0.06
Australia. Victoria	2574901	1983 -2007 (25)	-0.810	**0.00**		-0.593	**0.01**
Colombia, Cali	1000036	1983 -2007 (25)	0.010	0.96		0.029	0.91
Italy, Romagna	577247	1988 -2007 (20)	-0.074	0.76		-0.192	0.43
Singapore, Chinese	1324700	1968 -2007 (40)	-0.558	**0.00**		-0.188	0.44
Denmark, all	2704655	1978 -2007 (30)	-0.930	**0.00**		-0.766	**0.00**
Philippines, Manila	2993487	1983 -2007 (25)	-0.371	0.07		-0.185	0.45
Italy, Torino	435148	1985 -2007 (23)	-0.341	0.11		0.048	0.84
Costa Rica, all	2227538	1980 -2007 (28)	-0.008	0.97		-0.419	0.07
USA, Calif, Los Angel, Blacks	450132	1973 -2007 (35)	-0.357	**0.04**		-0.155	0.53
France, Isere	585746	1979 -2007 (29)	0.045	0.82		0.129	0.60
USA, Calif, Los Angel, His Whites	2220592	1973 -2007 (35)	-0.457	**0.01**		-0.076	0.76

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Worldwide Inverse Association between Gastric Cancer and Esophageal Adenocarcinoma Suggesting a Common Environmental Factor Exerting Opposing Effects

Short Title:
Association of esophageal adenocarcinoma & gastric cancer

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MHD: Design, analysis and intellectual input; **MA**: Analyses and intellectual input; **DHB**: Design and intellectual input; **JJG**: Intellectual input; **DRM**: intellectual input; **DF**: Design and intellectual input; **KELMcC**: Concept of idea and overall supervision.

This study was funded by an NHS Greater Glasgow Endowment Fund, UK

Text word count: 3,860. Tables & Figures: 7, References 36.

Supplement: Tables: 1, Figures: 4

Conflicts of interests: None to declare

Abbreviations:
EAC: Esophageal Adenocarcinoma; CGC: Cardia Gastric Cancer;
NCGC: Non-Cardia Gastric Cancer; TGC: Total Gastric Cancer;
WASR: World Age Standardised Incidence Rate;
AAPC: Average Annual Percentage Change.

ABSTRACT

Objectives: The incidence of esophageal adenocarcinoma (EAC) is increasing while adenocarcinoma of the stomach is decreasing. We have investigated whether the incidences of these two cancers and their time trends might be inversely related pointing to a common environmental factor exerting opposite effects on these cancers.

Methods: For cross-sectional analyses data were abstracted from "Cancer Incidence in Five Continents" (CI5) Volume X and GLOBOCAN 2012. Relevant ICD-10 codes were used to locate esophageal and gastric cancers anatomically, and ICD-O codes for the histological diagnosis of EAC. For longitudinal analyses age standardised rates (ASR) of EAC and total gastric cancer (TGC) were extracted from CI5C-Plus.

Results: Estimated (2012) ASRs were available for 51 countries and these showed significant negative correlations between EAC and both TGC (males: CC=-0.38, p=0.006, females: CC=-0.41, p=0.003) and non-cardia gastric cancer rates (males CC= -0.41, p=0.003 and females CC=-0.43, p=0.005). Annual incidence trends were analysed for 38 populations through 1989-2007 and showed significant decreases for TGC in 89% and increases for EAC in 66% of these, with no population showing a fall in the latter. Significant negative correlation between the incidence trends of the two cancers was observed in 28 of the 38 populations over the 19-50 years of available paired data. Super-imposition of the longitudinal and cross-sectional data indicated that populations with a current high incidence of EAC and low incidence of gastric cancer had previously resembled countries with a high incidence of gastric cancer and low incidence of EAC.

Conclusion: The negative association between gastric cancer and EAC in both current incidences and time trends is consistent with a common environmental factor predisposing to one and protecting from the other.

Key words: Esophageal adenocarcinoma, Gastric cancer, Incidence, Negative correlation, Epidemiology, Atrophic gastritis, *Helicobacter pylori*.

STUDY HIGHLIGHTS

WHAT IS CURRENT KNOWLEDGE

- The incidence of esophageal adenocarcinoma (EAC) is increasing rapidly in Western populations.
- The incidence of gastric cancer is decreasing throughout the world.

WHAT IS NEW HERE

- We have demonstrated an inverse relationship between the current incidences of those two cancers for countries throughout the world.
- We have demonstrated an inverse relationship between the incidence trends of the two cancers within individual cancer registries.
- Countries with a current high incidence of EAC and low incidence of gastric cancer previously resembled countries with a current low incidence of EAC and high incidence of gastric cancer.
- The inverse association between these two cancers is consistent with changes in the prevalence of a common environmental factor predisposing to one and protecting from the other.

INTRODUCTION

Over the past three decades, esophageal adenocarcinoma (EAC) has been one of the fastest increasing malignancies in many countries[1,2]. The cancer is thought to be the result of gastroesophageal reflux damaging the distal esophagus and causing columnar metaplasia often with intestinal phenotype. This Barrett's mucosa has an increased risk of progressing to dysplasia and adenocarcinoma.

The environmental factors causing the recent marked increase in incidence of EAC are unclear. Central obesity is associated with both reflux and EAC and the increasing prevalence of obesity is likely to explain some of the rise in incidence of EAC [(3,4)]. Smoking is another well-established risk factor for esophageal adenocarcinoma [5]. However, the prevalence of smoking has decreased over more than six decades in most Western countries and thus this cannot account for more recent increases in incidence of esophageal adenocarcinoma [6].

Another possible explanation is that *H.pylori* infection has been protecting against acid reflux, and thus EAC, and this is being lost by the falling incidence of the infection[7]. There is a well-established negative association between *H.pylori* infection and both gastroesophageal reflux and EAC.[8,9] This negative association between *H.pylori* and EAC is independent of the other risk factors of EAC including smoking and BMI[10]. A proposed mechanism for the protective effect of *H.pylori* is that the gastritis induced by it may cause atrophy and reduced acid secretory capacity of the gastric mucosa. As the acidity of the gastric juice is its main damaging component, reduction of this by *H.pylori* would protect against reflux-induced esophageal damage and associated adenocarcinoma[11].

H. pylori atrophic gastritis is the major risk factor for non-cardia gastric cancer (NGGC)[(12)]. If *H.pylori* infection does protect against EAC by inducing atrophy and reduced acid secretion, there should be a negative association between NCGC and EAC at a population level as the gastric mucosal changes predisposing to gastric cancer would be the same as those protecting from EAC.

Opposing incidence trends for EAC and NCGC have been reported in a study of the population of the East of England [13].

This study examined the relationship between the current incidences of the two cancers in different geographical regions of the world. In addition, we studied the relation between changes in incidence of the two cancers over time.

MATERIALS & METHODS

Cross-Sectional Studies

Based on data from Cancer Incidence in Five Continents Vol. X (CI5X) [14] and GLOBOCAN 2012 [15], age-specific and age-standardized (world population) incidence rates (WASR) were estimated for EAC and gastric cancer by topographical subsite (cardia and non-cardia) in 2012. This method has been described in more detail by Arnold et al.[16] and Colquhoun et al.[17] In brief, sex- and age-specific (<65; ≥65 years) proportions of EAC were computed for all countries included in CI5X except for those with no cases of EAC in one of four substrata (male, female; <65, ≥65 years) (N=51). Similarly, the proportions of cardia cancer (C16.0) and NCGC (C16.1-6) cases out of all gastric cancers with known topography (C16.0-6) were calculated for each country included in CI5X and stratified by sex and the same broad age groups, provided there were two or more cases of cardia cancer (CGC) and NCGC within each sex and age group stratification. Where there were multiple datasets (from different regional cancer registries within a country), cases and populations were pooled to obtain estimated national proportions. The histological types of esophageal cancer and the topographical classification of gastric cancers were defined according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3) presented in Cancer Incidence in Five Continents Vol. IX (CI5IX) [18,19]. For this analysis, the national or regional proportions of CGC/NCGC and EAC cases determined in the previous steps were applied to the 2012 gastric and EAC incidence estimates in GLOBOCAN 2012. Age-standardized incidence rates were computed using the world standard population (Table 1).

Longitudinal Studies

For the longitudinal study, WASR of EAC and total gastric cancer (TGC) were extracted from Cancer Incidence in Five Continents-Plus (CI5-plus) [1]. Cardia and non-cardia subsite data were not used because there were few longitudinal data for the specific subsite and also because there have been continuous changes in the subsite assignation practices for gastric cancer in histopathology laboratories. A total of 38 populations around the world were selected for this study based on **a**) availability of data of esophageal cancer recorded by histology, **b**) a time period of at least 19 years ending in 2007, **c**) if separate datasets were available for ethnic groups, at least one dataset per ethnic group was selected. The incidence (WASR) of EAC and TGC at the start year (different for each registry), year 1989 (earliest time common for all populations) and year 2007 (end year) were reported in Table 2, for men and women separately.

Statistical Analyses

For the cross-sectional study, Spearman's rho correlations were used to explore the relationship between WASR of the two cancers. In the longitudinal study, in addition to Spearman's rho correlations for pairwise correlation of EAC and TGC, time trends for individual registries, regression modelling was used to estimate the degree of incidence changes over time as described by Kim et al [20]. Briefly, using Joinpoint Programme version 4.1.0 (National Cancer Institute, USA) we analysed the time trend data for each cancer, in each registry, in men and women individually (38 x2 x2= 152 datasets). The programme fitted the simplest Joinpoint model that the data allowed. The models used the log of the WASR for calculating the average annual percent change (AAPC) in rates and their corresponding 95% confidence intervals. When any comparisons were made between different populations, the AAPC was always limited to the same 19 year period (1989-2007). When correlations were made between the change of cancer incidence between the two cancers within the same population, we present this in two different forms, firstly for the full

length of available longitudinal data for each population and secondly, limiting it to the same common observation period (1989-2007).

As EAC is much more common in men, we have focused mainly on results for men within the main text but have provided comparable analyses for women in the supplement.

RESULTS

A. Cross-sectional Study of National data

Incidence rate estimates were available for 51 countries (Table 1). There was a wide range in the rates of both gastric cancer and EAC across these different countries. The incidence of EAC varied from 0.23 per 100,000 person-years to 7.24. The incidence of TGC varied from 2.84 to 62.26 and that of NCGC from 1.75 to 58.64. In general terms, gastric cancer incidence was highest in East Asia and lowest in Western Europe and North America whereas EAC showed the opposite trend. In all 51 countries except the UK, EAC incidence rates were lower than the TGC rates and in 43 of 51 countries also lower than the NCGC incidence rate.

Statistically significant negative correlations between the incidence rates of EAC and both TGC {men (CC= -0.38, p=0.006), women (CC= -0.41, p=0.003)} and NCGC incidence {men (CC= -0.41, p=0.003) and women (CC= -0.43, p=0.005)} were observed.

The wide range in incidence of both EAC and TGC together with their inverse correlation resulted in a more than 200-fold range in the ratios of TGC to EAC across the different countries (more than 200:1 for the Republic of Korea to less than 1:1 for the UK)

Despite the strong negative correlation between the incidence rates of the two cancers, inspection of the data points indicated that in two respects the correlation was not linear (Fig. 1a.b). Firstly, the incidence of EAC seemed to be at a similar low level for all countries with moderate or high gastric cancer incidence and with a progressive rise in incidence at lower gastric cancer levels. The incidence of TGC below which the rise in EAC was apparent was approximately 15 per 100,000p/y in men (Fig. 1) and 7.5 per 100,000p/y in women (Fig. S1a,b). Secondly, when the incidence of TGC was low, the level of EAC incidence varied

considerably between countries with some showing marked elevation, some moderate and some no elevation. The equivalent figures for women showed a similar pattern though this was less clear due to much lower incidence rates (see Fig. S1a,b in supplement).

In order to investigate further the geographical distribution of the countries according to their TGC and EAC incidence rates, we sub-divided them into 4 groups (Fig. 1c). In men, the first 3 groups consisted of countries with low TGC incidence (<15 per 100,000 p/y) and EAC incidence high (>5) - Group A, medium (1.5-5) - Group B, and low (<1.5) – Group C. The fourth group (D) consisted of countries with high rates of gastric cancer (>15) and low EAC (<1.5).

The countries in these different groupings are shown in Figure 2. Group A with the highest rate of EAC and low (<15) TGC was limited to the UK, the Netherlands and Ireland. Group B with moderate EAC and low TGC (<15) comprised Northern America, Australia, New Zealand, Germany, Belgium, Denmark, Finland, Norway, France, Brazil and Uruguay. Area C with low EAC and low TGC (<15) was a very heterogeneous group from around the world (Thailand, Phiippines, India, Bulgaria, Croatia, Egypt, Israel, Italy, Spain, Poland, Serbia, Slovakia, Singapore); Group D with low EAC and moderate to high TGC includes South American countries, Eastern Europe, Korea, China, Japan, Russia, Iran and Turkey.

In women, sub-dividing all countries into groups based on their rates of esophageal and gastric cancer incidence demonstrated similar geographical patterns (Fig S2 in supplement).

B. Longitudinal Study

B1. Changes in incidence of esophageal adenocarcinoma and gastric cancer

To explore the rate of change in incidence of EAC and TGC during the period of 1989-2007 in males, we calculated average annual percentage change (AAPC) for each of the 38 populations individually, and presented these in Fig. 3, ordered by the most recent incidence of EAC. During this time period, most populations (34/38, 89%) had experienced a significant decrease in the incidence of TGC, with these 34 showing a range of AAPC from -

1.4% (95% CI: -2.1, -0.6 in Japan, Miyagi) to -5.1% (95% CI: -5.8, -4.3) in Austria, Tyrol. Twenty-five of 38 (66**%**) populations showed a significant increase in incidence of EAC during the period of observation and no population showed a significant fall in incidence (Fig. 3). Annual increases in EAC incidence ranged from 1.5% (95% CI: 0.8, 2.3 in Victoria, Australia) to 11.7% (95% CI: 3.7, 20.2 in Estonia).

We investigated any differences between the 13 populations showing no significant rise in EAC and the 25 population showing a rise. The populations which showed no significant change in EAC showed a rate of decrease in TGC (AAPC range -4.9% to 0.7%) similar to those that showed increase in EAC (AAPC range = -5.1% to -1.4%), (p=0.504). Likewise, the registries showing no rise in EAC did not differ from those showing an increase in that the two groups had a similar most recent (2007) TGC incidence (9.5 vs 9.6/1000,000py; p=0.584).

The data for women again showed a similar pattern and are shown in Fig S3. Additionally, further analyses using longer but varying periods of observation (19-50 years) were conducted with similar findings and are presented in the supplement as Fig S4 for men only.

B2. Correlation of Incidence trends of EAC and TGC

We looked for any correlation between the incidence trends for both cancers for those 38 populations with sufficient longitudinal data and included the full observation period of paired data (ie not limited to 1989-2007) (Table 3). In men, significant negative correlations between incidence rate trends of EAC and TGC over time were present in 27 of the 38 populations when compared over preceding 19-50 years and evaluated in pairs (Table 3). Positive correlations were not observed for any population.

When the calculation of correlations between EAC and TGC incidence trends was limited to the common but shorter observation period (last 19 years of 1989-2007), the magnitude of correlations was weaker in some of the populations. Only 19 of 38 populations showed

significant negative correlations for men and 7 of 38 for women (see Table S2 in supplement).

C. Relationship of longitudinal and cross-sectional data

We investigated the relationship between the cross-sectional data of most recent incidences of the two cancers and the longitudinal incidence trends. On the cross-sectional scatter plot figure showing the correlation between current incidence of EAC and TGC across different countries we superimposed a line indicating the incidence trend over preceding years available from the longitudinal data. This allowed us to examine the changes in incidence of both TGC and EAC cancer over time and how it related to their current incidences in different countries. To facilitate visual inspection we did this separately for each of the four categories of countries i.e. groups A,B,C and D based on incidence pattern of the two cancers (Fig. 4). For the longitudinal data we selected the 3 populations from each of groups A, B, C and D with the longest observation periods.

The resulting plots indicated that the countries with current low incidence of TGC and current high, medium or low incidence of EAC had previously resembled countries with a current high incidence of TGC and current low incidence of EAC. As the incidence of TGC has fallen this has been accompanied by varying degrees of increase in EAC with some populations showing a marked increase, some moderate increase and some no increase.

DISCUSSION

Our study has demonstrated an inverse association between the incidence of EAC and gastric cancer. This is apparent with respect to both the current incidences of these two cancers across different countries and with respect to changing incidence of the two cancers within the same populations over time. The inverse association is intriguing in view of the fact that the two cancers are biologically very similar. Both EAC and TGC arise from epithelia of closely adjacent, indeed abutting regions of the upper gastrointestinal tract, both

are the result of chronic damage and inflammation exerted by their luminal environment and both usually show very similar and often indistinguishable histological appearance.

Our cross-sectional study showed that both cancers were similar in having a wide range in current incidence rates (20-30 fold in males) across the different countries but different in having contrasting geographical patterns. The longitudinal studies showed that the incidences of both TGC and EAC had changed markedly over recent decades but these changes were in opposite directions and there was a statistically significant inverse association between the changing incidence rates of the two cancers in 71% of the registries.

Combining the cross-sectional and longitudinal data provided an overall picture of what has been happening to these two cancers over time and in different regions of the world. Previously, most countries had a high incidence of gastric cancer and a low incidence of EAC. Since then, the incidence of gastric cancer has fallen in all countries and as it has reached low levels it has been accompanied by varying degrees of increase in EAC with some regions showing marked increase, some moderate and others no increase.

What is the explanation for the opposing incidences and time trends of these two cancers? Could differences between countries in classification of junctional cancers into esophageal versus gastric locations and/or changes in classification of these cancers over time explain some of the observations? In the cross-sectional study, we found that the inverse association remained strong and indeed became slightly stronger by excluding cancers occurring at the gastric cardia and thus more likely to be misclassified. The longitudinal data only provided information on TGC. Spurious inverse association between incidence trends of the two cancers due to changing classification of cardia junctional cancers would only be likely to be a significant issue in countries with a very high incidence of gastric cancer and low incidence of EAC as misclassification of a small proportion of the former could substantially increase the latter[21]. Such misclassification, however, could not explain the strong inverse incidence trends as they were most apparent in countries with lower gastric cancer incidence [22].

The marked changes in incidence of TGC and EAC over a short time scale indicate the influence of a changing environmental factor. In addition, the inverse association between the changing incidences indicates that the environment factor is exerting opposite effects on these two cancers. The environmental factors which are thought to explain the falling incidence of TGC include a falling incidence of *H. pylori* atrophic gastritis, dietary changes and reduced smoking [23,24]. Could the falling incidence of any of these be associated with an increase in EAC and thus explain the inverse association in the incidence trends of the two cancers? Smoking is not a candidate as it is a similar risk factor for both cancers [5,25]. Dietary changes might be important. There is some evidence that increased intake of vitamins and reduced salt consumption may have contributed to the falling incidence of gastric cancer [26,27]. These specific dietary factors would not in themselves explain the increase in EAC and indeed increased vitamin consumption may protect from EAC [28]. However, increased caloric intake and associated obesity is a well-established risk factor for EAC [28]. It is therefore possible that changes in the diet comprising both a fall in salt content and increased caloric content could produce a fall in total TGC and rise in EAC. However, a recent analysis indicated that increasing obesity may only account for 6.5% of the increase in incidence of EAC and suggesting the role of additional environmental factors [3].

Another environmental factor which might exert opposite effects on the incidence of the two cancers is *H. pylori* atrophic gastritis which is the most important etiological factor for NCGC [29]. In countries with a high incidence of gastric cancer there is also a high incidence of atrophic gastritis and associated impaired gastric acid secretion [30]. In contrast, in subjects without *H.pylori,* gastric acid is maintained and shows no decline with increasing age[31]. In countries with a high incidence of gastric cancer the high prevalence of *H.pylori* atrophic gastritis will protect from EAC as any gastroesophageal refluxate will have reduced ability to damage the esophagus due to its reduced acidity. Epidemiological studies have shown consistent associations between *H. pylori* and both TGC and EAC being positive with respect to the former and negative with respect to the latter [10]. As the prevalence of *H.pylori* atrophic gastritis falls, it will be accompanied by a fall in gastric cancer but

potentially also a rise in EAC due to increasing gastric acidity. The prevalence of *H. pylori* infection has fallen over recent decades in association with improved living conditions [32].

Interactions between *H. pylori* and dietary factors might also be important. There is some evidence that a high vitamin, low salt diet may protect from the development of atrophic gastritis in *H. pylori* infected subjects [33]. Improved living conditions, with accompanying fall in *H. pylori* prevalence as well as increased vitamin and reduced salt intake could together markedly reduce atrophic gastritis with resultant fall in TGC and increase in EAC.

In the previous study by Anderson et al showing a strong negative association between *H.pylori* and esophageal adenocarcinoma, the association persisted even after correcting for atrophic gastritis detected by serum pepsinogens [8]. However, it is recognised that serum pepsinogens are insensitive markers of atrophy[34]. In addition, *H.pylori* body-predominant gastritis is associated with reduced gastric acid secretion independent of atrophy.[35] Furthermore, body-predominant gastritis is an important risk factor for gastric cancer[36] so even without significant atrophy it might both promote gastric cancer and protect from esophageal adenocarcinoma.

Though there were strong inverse associations between the two cancers with respect to both current incidences and time trends, there was a group of countries with a low incidence of both cancers. This was a heterogeneous group consisting of Thailand, Philippines, Singapore, India, Egypt, Israel, Bulgaria, Croatia, Italy, Spain, Poland, Serbia and Slovenia. Due to the limited availability of longitudinal data for many of these populations, it was difficult to determine whether their low incidence of both cancers was due to the absence of a rise in EAC as their incidence of TGC fell, or whether they had never had a high incidence of TGC and were somehow protected from both cancers. It is possible that genetic and/or environmental factors present in some of these populations might inhibit the progression from inflammation to neoplasia which is a common final step in the pathways leading to both TGC and EAC. A lack of increase in EAC despite TGC falling to a low level might be due to genetic and/or environmental factors protecting from gastroesophageal reflux which is an

essential early step in the pathway to EAC. Comparative studies of countries with low versus high incidence of EAC despite low incidence of TGC may shed new light on the etiology and pathogenesis of EAC.

An important question is whether countries where gastric cancer incidence is still high but falling such as Japan and South East Asia will encounter a rise in EAC similar to that recently experienced in Western countries. A fall in the incidence of gastric cancer to a low level is not necessarily accompanied by a rise in esophageal adenocarcinoma as highlighted above. However, the current incidence of gastric cancer in Japan and South East Asia is still at a level which when present in Western countries was not yet associated with any rise in EAC and it will be interesting to observe what happens when this point is reached.

Strengths of our study include the use of high quality global surveillance data. Limitations also need however to be recognised. Incidence rates used in the cross-sectional analysis were based on country-, age- and sex-specific proportions of EAC from CI5X, which were then applied to GLOBOCAN 2012 data. Hence, they represent estimates of the true incidence rates within each country and should be interpreted with caution. Our inclusion criteria for the cross-sectional study furthermore resulted in a selection of 51 mostly high-income countries, which may not be fully representative on the global level. Pathological practices and classifications of histological subtypes have changed over time, which should be kept in mind when interpreting the results, especially from the longitudinal analyses. Also, registries covering different time periods (19 to 50 years) were included in some of the longitudinal analysis, making them not directly comparable. Finally, most of the countries included in the cross-sectional studies have more than one original cancer registry and even though we selected the largest registry available from each country, it may not represent the full national picture.

In conclusion, this study demonstrates a strong inverse association between gastric cancer and EAC with respect to both their current incidences and time trends, suggesting a changing common environmental influence exerting opposite effects on these two cancers. Though ecological studies do not establish causality, one biologically plausible

environmental factor which could explain this unusual inverse association is *H. pylori* atrophic gastritis. However, changes in disease incidence are usually the result of several interacting environmental factors and changes in lifestyle predisposing to obesity as well as dietary interactions with *H. pylori* to induce atrophy are also likely to be important.

FIGURE LEGENDS

Fig 1: Correlations between incidence rates (WASR) of EAC and gastric cancer in cross-sectional study in men.
Note: Each dot represents a dataset from a country, 1a: EAC versus total gastric cancer, 1b. EAC versus non-cardia gastric cancers, 1c: visual clustering of countries divided into groups A-D.

Fig 2: Maps of countries colour-coded with visual clustering of populations with different combinations of EAC and gastric cancer in cross-sectional study in men.
Note: For each country, a pooled national data has been used to create colour codes. The grey code indicates no data available. **A:** TGC<15 & EAC≥5, **B:** TGC<15 & 1.5≤EAC<5, **C**: TGC<15 & EAC<1.5, **D:** TGC≥15 & EAC<1.5.

Fig 3: Average Annual Percentage Changes (95% CI) of EAC versus TGC in men during short common period (1989-2007) of registration in populations.

Fig 4: Longitudinal data superimposed on cross-sectional cancer incidence by groups A-D in men.
Incidence of esophageal adenocarcinoma is shown on Y axis (per 100,000py) and incidence of total gastric cancer on X axis. The cross-sectional data of the most recent cancer incidence for different countries is shown by dots. For the three populations with the longest available longitudinal data, we have superimposed on the dot diagram a line indicating their incidence trend from start to end of registration period dates. The dates of the start and end of the incidence trend line is given above in box and the time-line is always from right to left.

Supplementary figures

Fig S1: Correlations between incidence rates (WASR) of EAC and gastric cancer in cross-sectional study in women.
Note: each dot represents a dataset from a country, 1a: EAC versus total gastric cancer, 1b. EAC versus non-cardia and other gastric cancers, 1c: visual clustering of countries divided into groups A-D.

Fig S2: Maps of countries colour-coded with visual clustering of populations with different combinations of EAC and gastric cancer in cross-sectional study in females.
Note: For each country, a pooled national data has been used to create colour codes. The grey code indicates no data available. **A:** TGC<7.5 & EAC≥1, **B:** TGC<7.5 & 0.3≤EAC<1, **C**: TGC<7.5 & EAC<0.3, **D:** TGC≥7.5 & EAC<0.3.

Fig S3: Average Annual Percentage Changes (AAPC) of EAC versus TGC in women during short common period (1989-2007) of registration.

Fig S4: Average Annual Percentage Changes (AAPC) of EAC versus TGC in men during full period (19-50 years) of registration.

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Table 1: Estimated age-standardised incidence rates (world) of gastric cancer and esophageal adenocarcinoma in different countries in cross-sectional study. The countries are listed based on incidence of Esophageal adenocarcinoma.

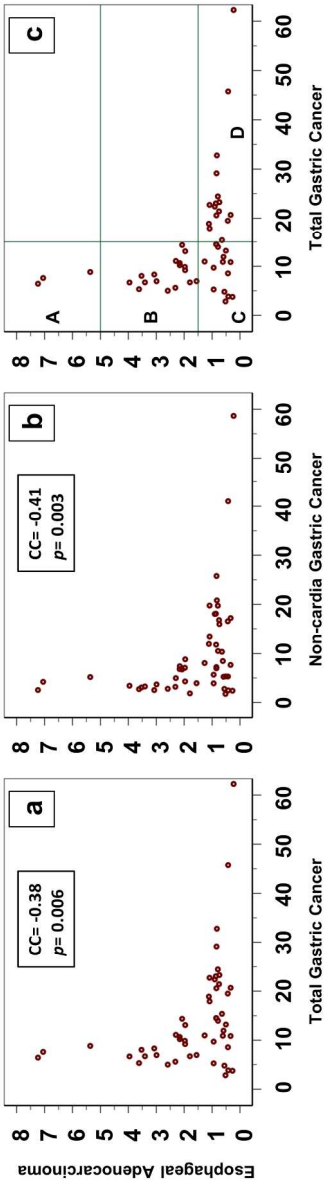
	Men					Women			
Country	**TGC**	**Cardia**	**NCGC**	**EAC**		**TGC**	**Cardia**	**NCGC**	**EAC**
United Kingdom	6.44	3.89	2.55	7.24		3.15	1.46	1.69	1.36
The Netherlands	7.61	3.39	4.22	7.05		3.9	1.03	2.86	1.19
Ireland	8.83	3.64	5.19	5.36		4.42	1.42	3	1.01
New Zealand	6.69	3.27	3.42	3.96		3.83	0.88	2.94	0.56
United States of America	5.33	2.6	2.73	3.62		2.7	0.66	2.04	0.42
Belgium	8.04	4.96	3.08	3.53		3.83	1.36	2.48	0.57
Australia	6.72	3.44	3.27	3.41		3.14	0.99	2.15	0.49
Denmark	8.32	5.79	2.53	3.07		3.05	1.27	1.78	0.76
Canada	6.95	3.26	3.69	2.99		3.12	0.83	2.29	0.42
Switzerland	5.01	2.21	2.8	2.59		3.58	0.89	2.69	0.49
Norway	5.61	2.41	3.2	2.32		3.82	0.91	2.91	0.43
Malta	11.08	6.1	4.98	2.3		5.53	1.2	4.33	0.11
Germany	10.66	3.84	6.82	2.16		5.44	1.01	4.43	0.28
Czech Republic	10.21	2.81	7.41	2.16		5.27	0.75	4.52	0.29
Uruguay	14.36	7.61	6.75	2.07		6.7	2.06	4.64	0.61
Argentina	9.87	2.79	7.08	1.98		4.19	0.71	3.48	0.44
Austria	9.2	4.89	4.31	1.97		4.83	1.42	3.41	0.23
Brazil	13.08	4.26	8.82	1.96		5.96	1.16	4.8	0.59
Finland	6.72	4.86	1.86	1.8		3.94	2.06	1.88	0.3
France (metropolitan)	6.97	3.03	3.94	1.56		2.8	0.48	2.32	0.33
Spain	10.97	2.91	8.05	1.27		5.11	0.66	4.45	0.18
Colombia	18.89	6.93	11.95	1.11		8.97	2.18	6.8	0.21
Lithuania	22.73	2.99	19.75	1.09		8.02	0.61	7.41	0.15
Turkey	17.92	4.49	13.43	1.09		10.93	2.34	8.59	0.21
Israel	9.71	4.03	5.68	0.94		4.9	1.45	3.45	0.2
Puerto Rico	5.28	1.37	3.91	0.94		3.11	0.48	2.64	0.26
Ukraine	22.39	4.36	18.03	0.9		9.14	1.29	7.85	0.16
Latvia	23.05	4.97	18.08	0.86		8.68	0.93	7.74	0.18
Bulgaria	14.51	2.71	11.8	0.86		6.99	0.88	6.12	0.12
Croatia	14.47	7.5	6.97	0.85		6.27	2.39	3.88	0.12
Iran, Islamic Republic of	20.6	13.37	7.22	0.85		9.72	5.4	4.32	0.85
Belarus	29.14	3.37	25.77	0.84		12.22	0.95	11.27	0.1
China	32.77	11.97	20.8	0.83		13.1	3.37	9.73	0.26
Russian Federation	24.45	4.74	19.71	0.79		10.8	1.58	9.21	0.13
Slovakia	13.95	3.43	10.52	0.79		6.58	0.92	5.66	0.15
Costa Rica	21.43	4.65	16.78	0.75		13.66	1.48	12.18	0.15
Chile	23.29	7.35	15.94	0.74		9.19	1.99	7.2	0.26
Slovenia	15.37	5.01	10.36	0.65		6.42	1.02	5.4	0.1
Italy	10.89	2.43	8.46	0.61		5.92	0.63	5.29	0.09
Serbia	11.94	6.69	5.25	0.59		5.68	2.94	2.75	0.14
Philippines	4.81	2.03	2.78	0.56		2.88	0.89	1.99	0.14
Egypt	2.84	1.09	1.75	0.52		2.27	0.55	1.72	0.28
Poland	13.19	7.87	5.32	0.5		4.95	2.08	2.86	0.09
Estonia	19.5	2.96	16.54	0.44		10.31	1.03	9.28	0.07
India	8.56	3.26	5.3	0.43		3.68	1.41	2.27	0.13
Japan	45.75	4.73	41.01	0.42		16.46	1.25	15.21	0.07
Saudi Arabia	3.84	1.36	2.48	0.42		2.41	0.72	1.69	0.15
Singapore	10.85	3.18	7.67	0.34		5.83	1.31	4.52	0.07
Ecuador	20.69	3.5	17.19	0.33		13.43	0.95	12.48	0.21
Thailand	3.77	1.36	2.41	0.27		2.49	0.8	1.68	0.08
Korea, Republic of	62.26	3.62	58.64	0.23		24.67	1.07	23.6	0.04

Table 2: List of recruited registries in longitudinal study, and incidence rates (WASR) of total gastric cancer and esophageal adenocarcinoma at the start, year 1989 and end of period

Study Population	Full-range Period (yrs)	Men						Women					
		EAC (start)	EAC (1989)	EAC (2007)	TGC (start)	TGC (1989)	TGC (2007)	EAC (start)	EAC (1989)	EAC (2007)	TGC (start)	TGC (1989)	TGC (2007)
Brazil, Goiania	1988 -2007 (20)	0.45	0.45	0.51	25.46	25.46	25.86	0.01	0.06	0.06	52.05	30.70	17.26
Estonia, all	1968 -2007 (40)	0.04	0.09	0.56	57.27	35.25	23.29	0.16	0.03	0.06	8.62	6.67	4.30
Thailand, Chiang Mai	1983 -2007 (25)	0.00	0.06	0.11	8.25	8.09	6.84	0.08	0.05	0.02	5.10	4.08	2.58
Switzerland, St Gall-Appenzell	1983 -2007 (25)	0.93	0.76	3.22	12.09	12.23	6.41	0.32	0.35	0.53	6.14	5.32	3.92
Israel, Jews	1963 -2007 (45)	0.06	0.08	0.86	24.84	13.26	9.58	0.00	0.05	0.17	8.63	7.96	7.01
Croatia, all	1988 -2007 (20)	0.26	0.26	0.63	28.98	28.98	17.36	0.02	0.04	0.09	19.41	10.89	7.19
Spain, Murcia	1983 -2007 (25)	0.74	1.21	1.44	17.88	15.67	10.46	0.09	0.02	0.24	5.96	5.02	3.31
Austria, Tyrol	1988 -2007 (20)	0.42	0.42	0.79	28.24	28.24	11.24	0.04	0.09	0.16	6.69	6.22	4.78
France, Bas-Rhin	1975 -2007 (33)	0.88	0.83	2.12	17.58	12.78	8.42	0.00	0.11	0.35	8.14	7.27	4.33
Spain, Granada	1985 -2007 (23)	0.58	0.39	1.16	17.77	14.92	10.02	0.03	0.03	0.22	16.40	16.40	6.93
Netherlands, all	1989 -2007 (19)	2.26	2.26	5.42	15.68	15.68	8.88	0.58	0.58	0.93	6.11	6.11	3.98
USA, Michigan, Detroit, Whites	1973 -2007 (35)	0.67	1.74	4.39	10.13	9.56	6.42	0.10	0.22	0.64	4.49	3.76	2.93
Switzerland, Vaud	1988 -2007 (20)	1.48	1.48	2.47	10.63	10.63	7.22	0.13	0.13	0.36	11.3	4.88	3.22
USA, Michigan, Detroit, Blacks	1973 -2007 (35)	0.30	0.48	1.03	16.24	16.10	12.08	0.04	0.05	0.19	14.78	6.19	5.20
Canada, Manitoba	1958 -2007 (50)	0.08	1.28	2.64	25.6	12.60	8.33	0.05	0.26	0.42	4.45	3.28	2.26
England, North West	1979 -2007 (29)	1.58	3.70	7.07	22.32	17.76	10.12	0.46	0.86	1.34	10.01	7.74	4.08
USA, SEER (9 Regs), Whites	1975 -2007 (33)	0.61	1.83	3.74	9.31	8.04	5.55	0.22	0.27	0.60	7.02	5.09	3.35
Scotland, all	1975 -2007 (33)	2.36	3.42	7.47	21.17	18.56	9.72	0.83	1.05	1.49	10.64	7.90	4.57
Australia, New South Wales	1983 -2007 (25)	0.71	1.54	2.67	12.36	10.82	7.54	0.00	0.26	0.50	8.03	6.46	3.68
Canada, Saskatchewan	1968 -2007 (40)	0.13	1.20	1.99	14.2	8.51	5.93	0.00	0.00	0.31	18.15	19.07	13.53
USA, Calif, Los Angel, Non-His Whites	1973 -2007 (35)	0.35	1.61	2.77	9.92	7.99	5.52	0.10	0.22	0.51	4.03	3.19	2.43
Japan, Osaka	1963 -2007 (45)	0.00	0.22	0.41	107.06	70.42	44.19	0.15	0.25	0.03	23.39	17.19	14.11
England, South & West	1979 -2007 (29)	1.40	3.46	5.84	17.21	14.79	7.02	0.30	0.48	1.11	6.99	3.77	2.72
Japan, Miyagi	1978 -2007 (30)	0.68	0.43	0.69	82.51	84.41	65.72	0.05	0.19	0.10	8.44	7.09	5.20
Slovakia, all	1973 -2007 (35)	0.15	0.35	0.78	42.30	25.06	16.43	0.00	0.04	0.15	8.29	5.40	3.80
India, Mumbai	1978 -2007 (30)	0.29	0.04	0.08	7.11	6.68	4.46	0.11	0.11	0.00	12.46	12.46	12.27
USA, SEER (9 Regs), Blacks	1975 -2007 (33)	0.17	0.46	0.74	15.30	15.04	10.43	0.00	0.00	0.14	23.97	23.97	10.48
Australia. Victoria	1983 -2007 (25)	1.23	1.74	2.64	14.84	12.33	7.97	0.12	0.20	0.45	5.27	4.40	3.47
Colombia, Cali	1983 -2007 (25)	0.19	0.68	0.87	32.46	33.40	25.82	0.00	0.07	0.18	7.82	6.31	4.81
Italy, Romagna	1988 -2007 (20)	0.44	0.44	0.45	41.78	41.78	20.34	0.23	0.05	0.03	38.26	34.52	22.21
Singapore, Chinese	1968 -2007 (40)	0.00	0.28	0.38	45.07	33.48	14.90	0.00	0.00	0.03	4.48	4.79	4.17
Denmark, all	1978 -2007 (30)	0.81	1.76	2.54	15.05	10.29	7.68	0.19	0.19	0.40	3.88	3.88	3.86
Philippines, Manila	1983 -2007 (25)	0.32	0.34	0.45	14.16	11.72	6.91	0.00	0.02	0.04	17.21	15.12	7.86
Italy, Torino	1985 -2007 (23)	0.41	0.55	0.82	20.25	19.18	10.65	0.00	0.00	0.16	8.94	9.15	5.40
Costa Rica, all	1980 -2007 (28)	0.55	0.52	0.63	48.40	39.53	24.65	0.08	0.08	0.08	11.87	11.87	7.22
USA, Calif, Los Angel, Blacks	1973 -2007 (35)	0.37	0.68	0.59	15.53	13.76	8.66	0.00	0.05	0.08	26.73	16.45	11.43
France, Isere	1979 -2007 (29)	0.33	1.98	1.51	13.26	14.81	7.36	0.04	0.05	0.28	6.81	3.54	3.01
USA, Calif, Los Angel, His Whites	1973 -2007 (35)	0.04	1.47	1.47	14.98	13.43	9.53	0.09	0.14	0.27	7.68	5.77	5.62

Table 3: Correlations between incidence (WASR) trends of esophageal adenocarcinoma and total gastric cancer In men in the two time periods- full range and 1989-2007.

Study Population	Population	Full Range				1989 - 2007	
	(2007)	Period (yrs)	CC	*P* value		CC	*P* value
Brazil, Goiania	588132	1988 -2007 (20)	0.048	0.84		0.098	0.70
Estonia, all	617828	1968 -2007 (40)	-0.420	**0.01**		-0.471	**0.04**
Thailand, Chiang Mai	741784	1983 -2007 (25)	-0.281	0.17		-0.109	0.66
Switzerland, St Gall-Appenzell	263298	1983 -2007 (25)	-0.590	**0.00**		-0.519	**0.02**
Israel, Jews	2674800	1963 -2007 (45)	-0.637	**0.00**		-0.173	0.48
Croatia, all	2137984	1988 -2007 (20)	-0.737	**0.00**		-0.713	**0.00**
Spain, Murcia	714667	1983 -2007 (25)	-0.394	0.05		-0.382	0.11
Austria, Tyrol	342794	1988 -2007 (20)	-0.530	**0.02**		-0.475	**0.04**
France, Bas-Rhin	534515	1975 -2007 (33)	-0.536	**0.00**		-0.458	**<0.05**
Spain, Granada	438332	1985 -2007 (23)	-0.442	**0.04**		-0.396	0.09
Netherlands, all	8100293	1989 -2007 (19)	-0.961	**0.00**		-0.971	**0.00**
USA, Michigan, Detroit, Whites	1390555	1973 -2007 (35)	-0.921	**0.00**		-0.821	**0.00**
Switzerland, Vaud	323759	1988 -2007 (20)	-0.402	0.08		-0.370	0.12
USA, Michigan, Detroit, Blacks	475552	1973 -2007 (35)	-0.271	0.12		0.193	0.43
Canada, Manitoba	588875	1958 -2007 (50)	-0.777	**0.00**		-0.402	0.09
England, North West	3223560	1979 -2007 (29)	-0.926	**0.00**		-0.800	**0.00**
USA, SEER (9 Regs), Whites	10682176	1975 -2007 (33)	-0.972	**0.00**		-0.834	**0.00**
Scotland, all	2485606	1975 -2007 (33)	-0.961	**0.00**		-0.913	**0.00**
Australia, New South Wales	3420484	1983 -2007 (25)	-0.888	**0.00**		-0.810	**0.00**
Canada, Saskatchewan	495639	1968 -2007 (40)	-0.724	**0.00**		-0.083	0.73
USA, Calif, Los Angel, Non-His Whites	1446148	1973 -2007 (35)	-0.843	**0.00**		-0.520	**0.02**
Japan, Osaka	4366616	1963 -2007 (45)	-0.915	**0.00**		-0.572	**0.01**
England, South & West	3442830	1979 -2007 (29)	-0.924	**0.00**		-0.774	**0.00**
Japan, Miyagi	1140676	1978 -2007 (30)	-0.383	**0.04**		-0.574	**0.01**
Slovakia, all	2621095	1973 -2007 (35)	-0.818	**0.00**		-0.463	**<0.05**
India, Mumbai	7479777	1978 -2007 (30)	-0.425	**0.02**		-0.567	**0.01**
USA, SEER (9 Regs), Blacks	1724091	1975 -2007 (33)	-0.592	**0.00**		-0.434	0.06
Australia. Victoria	2574901	1983 -2007 (25)	-0.810	**0.00**		-0.593	**0.01**
Colombia, Cali	1000036	1983 -2007 (25)	0.010	0.96		0.029	0.91
Italy, Romagna	577247	1988 -2007 (20)	-0.074	0.76		-0.192	0.43
Singapore, Chinese	1324700	1968 -2007 (40)	-0.558	**0.00**		-0.188	0.44
Denmark, all	2704655	1978 -2007 (30)	-0.930	**0.00**		-0.766	**0.00**
Philippines, Manila	2993487	1983 -2007 (25)	-0.371	0.07		-0.185	0.45
Italy, Torino	435148	1985 -2007 (23)	-0.341	0.11		0.048	0.84
Costa Rica, all	2227538	1980 -2007 (28)	-0.008	0.97		-0.419	0.07
USA, Calif, Los Angel, Blacks	450132	1973 -2007 (35)	-0.357	**0.04**		-0.155	0.53
France, Isere	585746	1979 -2007 (29)	0.045	0.82		0.129	0.60
USA, Calif, Los Angel, His Whites	2220592	1973 -2007 (35)	-0.457	**0.01**		-0.076	0.76



Correlations between incidence rates (WASR) of EAC and gastric cancer in cross-sectional study in men.
Note: Each dot represents a dataset from a country, 1a: EAC versus total gastric cancer, 1b. EAC versus non-cardia gastric cancers, 1c: visual clustering of countries divided into groups A-D.

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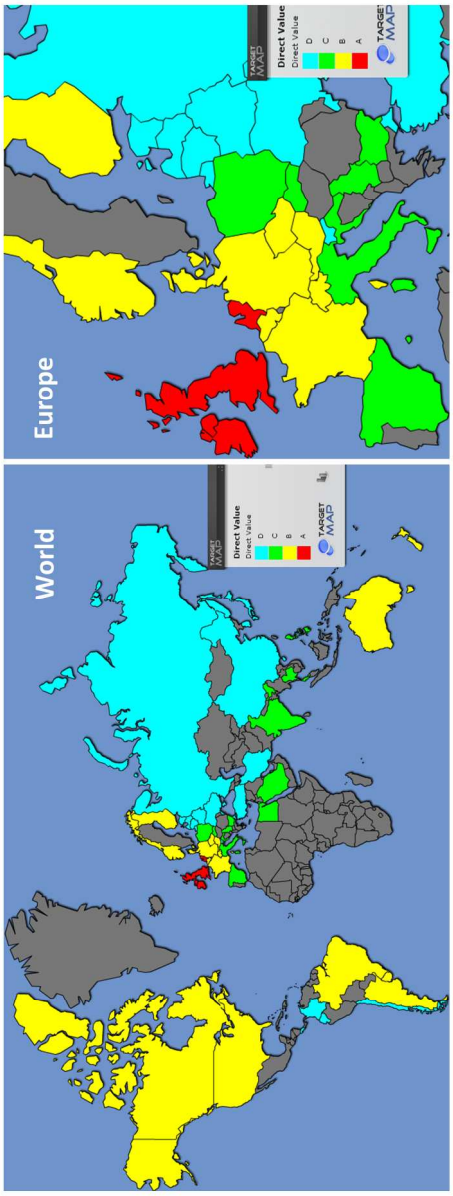

Maps of countries color-coded with visual clustering of populations with different combinations of EAC and gastric cancer in cross-sectional study in men.
Note: For each country, a pooled national data has been used to create colour codes. The grey code indicates no data available. A: TGC<15 & EAC≥5, B: TGC<15 & 1.5≤EAC<5, C: TGC<15 & EAC<1.5, D: TGC≥15 & EAC<1.5.

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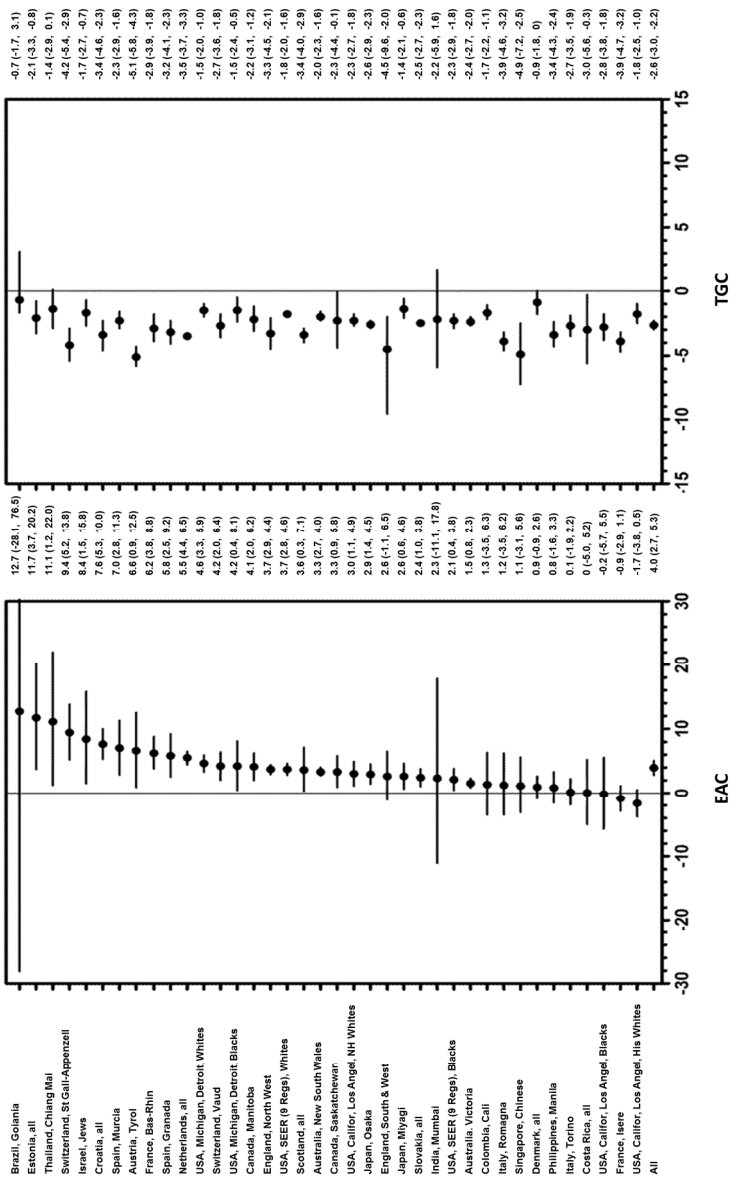

Average Annual Percentage Changes (95% CI) of EAC versus TGC in men during short common period (1989-2007) of registration in populations.
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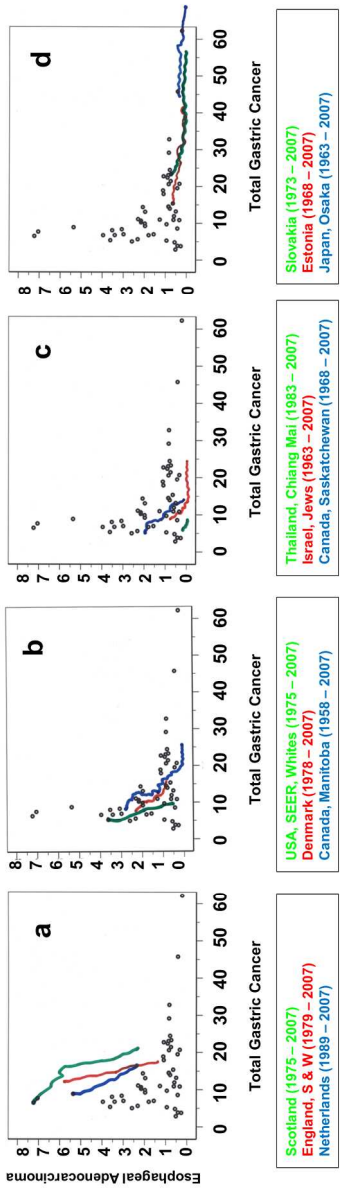


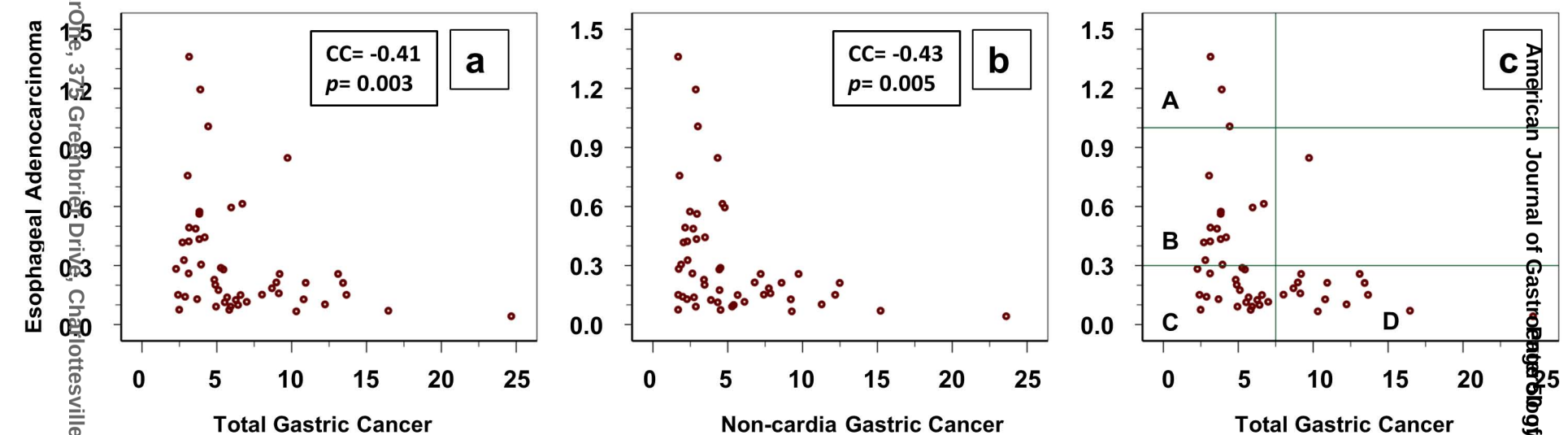
Longitudinal data superimposed on cross-sectional cancer incidence by groups A-D in men. Incidence of esophageal adenocarcinoma is shown on Y axis (per 100,000py) and incidence of total gastric cancer on X axis. The cross-sectional data of the most recent cancer incidence for different countries is shown by dots. For the three populations with the longest available longitudinal data, we have superimposed on the dot diagram a line indicating their incidence trend from start to end of registration period dates. The dates of the start and end of the incidence trend line is given above in box and the time-line is always from right to left

258x878mm (300 x 300 DPI)

Supplementary Tables and Figures (revised on 22 Oct 2015)

Table S1: Correlations between incidence (WASR) trends of esophageal adenocarcinoma and total gastric cancer in women in the two time periods- full range and 1989-2007.

Study Population	Period (yrs)	Full Range			1989-2007	
		CC	*P* value		CC	*P* value
Brazil, Goiania	1988 -2007 (20)	0.071	0.77		-0.077	0.76
Estonia, all	1968 -2007 (40)	-0.428	**0.01**		-0.243	0.32
Thailand, Chiang Mai	1983 -2007 (25)	-0.463	**0.02**		-0.514	**0.02**
Switzerland, St Gall-Appenzell	1983 -2007 (25)	-0.270	0.19		-0.130	0.60
Israel, Jews	1963 -2007 (45)	-0.477	**0.00**		0.086	0.73
Croatia, all	1988 -2007 (20)	-0.155	0.51		-0.272	0.26
Spain, Murcia	1983 -2007 (25)	-0.014	0.95		0.122	0.62
Austria, Tyrol	1988 -2007 (20)	-0.159	0.50		-0.251	0.30
France, Bas-Rhin	1975 -2007 (33)	-0.523	**0.00**		-0.234	0.33
Spain, Granada	1985 -2007 (23)	-0.348	0.10		-0.222	0.36
Netherlands, all	1989 -2007 (19)	-0.853	**0.00**		-0.860	**0.00**
USA, Michigan, Detroit, Whites	1973 -2007 (35)	-0.716	**0.00**		-0.384	0.10
Switzerland, Vaud	1988 -2007 (20)	-0.104	0.66		0.011	0.97
USA, Michigan, Detroit, Blacks	1973 -2007 (35)	-0.295	0.09		-0.283	0.24
Canada, Manitoba	1958 -2007 (50)	-0.486	**0.00**		-0.175	0.47
England, North West	1979 -2007 (29)	-0.778	**0.00**		-0.452	0.05
USA, SEER (9 Regs), Whites	1975 -2007 (33)	-0.863	**0.00**		-0.612	**0.01**
Scotland, all	1975 -2007 (33)	-0.860	**0.00**		-0.400	0.09
Australia, New South Wales	1983 -2007 (25)	-0.680	**0.00**		-0.573	**0.01**
Canada, Saskatchewan	1968 -2007 (40)	-0.270	0.09		0.168	0.49
USA, Calif, Los Angel, Non-His Whites	1973 -2007 (35)	-0.730	**0.00**		-0.408	0.08
Japan, Osaka	1963 -2007 (45)	-0.667	**0.00**		-0.292	0.23
England, South & West	1979 -2007 (29)	-0.944	**0.00**		-0.849	**0.00**
Japan, Miyagi	1978 -2007 (30)	-0.171	0.37		0.237	0.33
Slovakia, all	1973 -2007 (35)	-0.607	**0.00**		-0.383	0.11
India, Mumbai	1978 -2007 (30)	-0.297	0.11		-0.529	**0.02**
USA, SEER (9 Regs), Blacks	1975 -2007 (33)	-0.429	**0.01**		-0.353	0.14
Australia. Victoria	1983 -2007 (25)	-0.610	**0.00**		-0.476	**0.04**
Colombia, Cali	1983 -2007 (25)	-0.373	0.07		-0.336	0.16
Italy, Romagna	1988 -2007 (20)	-0.470	**0.04**		-0.421	0.07
Singapore, Chinese	1968 -2007 (40)	-0.237	0.14		-0.096	0.70
Denmark, all	1978 -2007 (30)	-0.731	**0.00**		-0.246	0.31
Philippines, Manila	1983 -2007 (25)	0.149	0.48		0.019	0.94
Italy, Torino	1985 -2007 (23)	-0.451	**0.03**		-0.251	0.30
Costa Rica, all	1980 -2007 (28)	0.143	0.47		0.244	0.31
USA, Calif, Los Angel, Blacks	1973 -2007 (35)	-0.316	0.06		-0.075	0.76
France, Isere	1979 -2007 (29)	-0.032	0.87		0.118	0.63
USA, Calif, Los Angel, His Whites	1973 -2007 (35)	-0.419	**0.01**		-0.310	0.20



Supp. Fig 1

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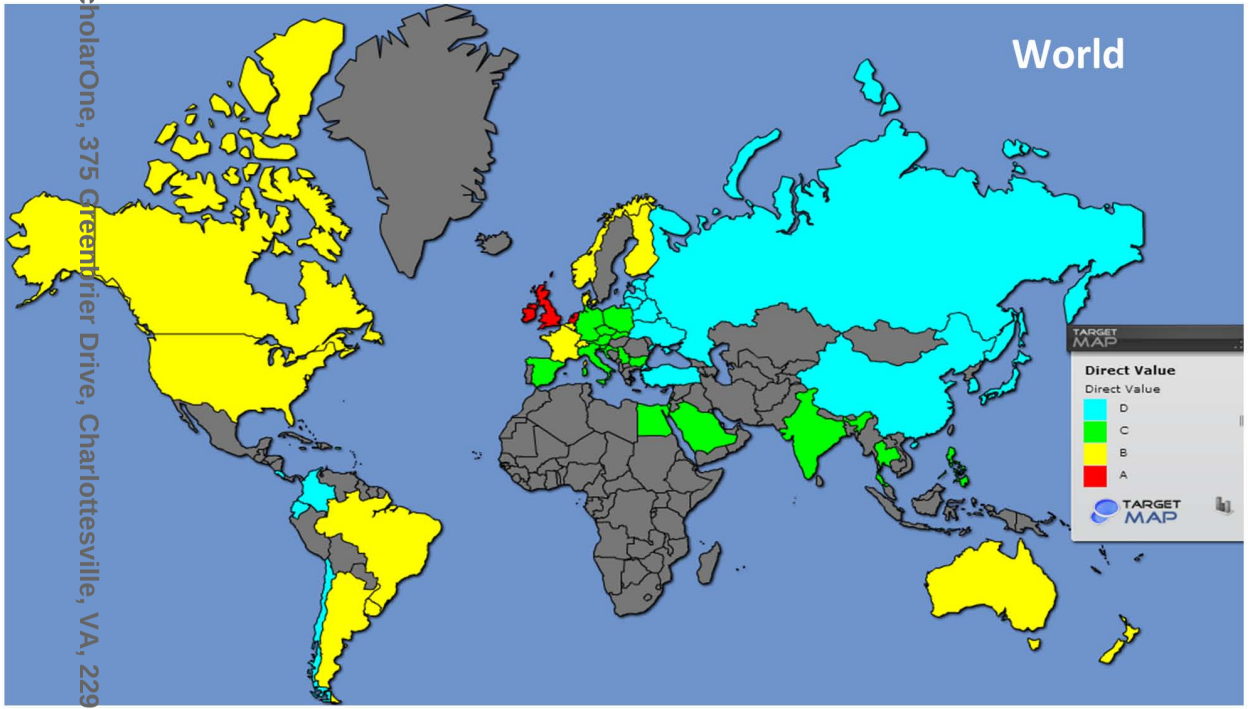

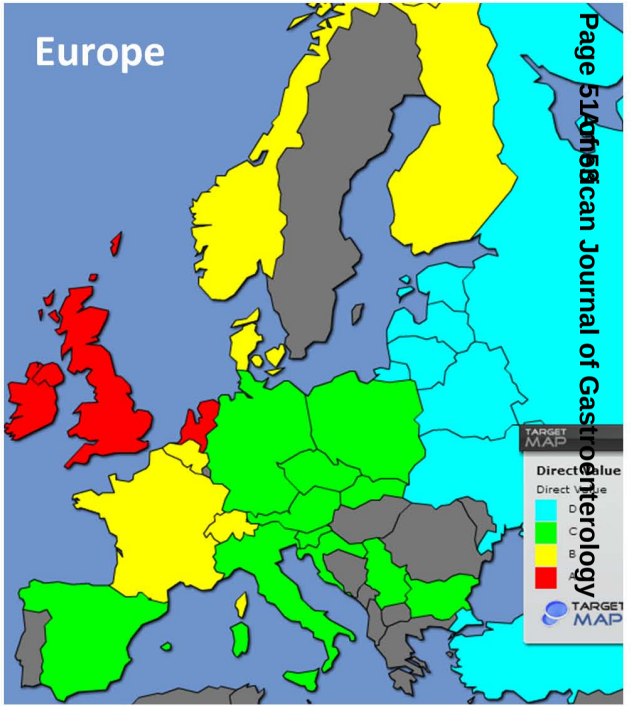

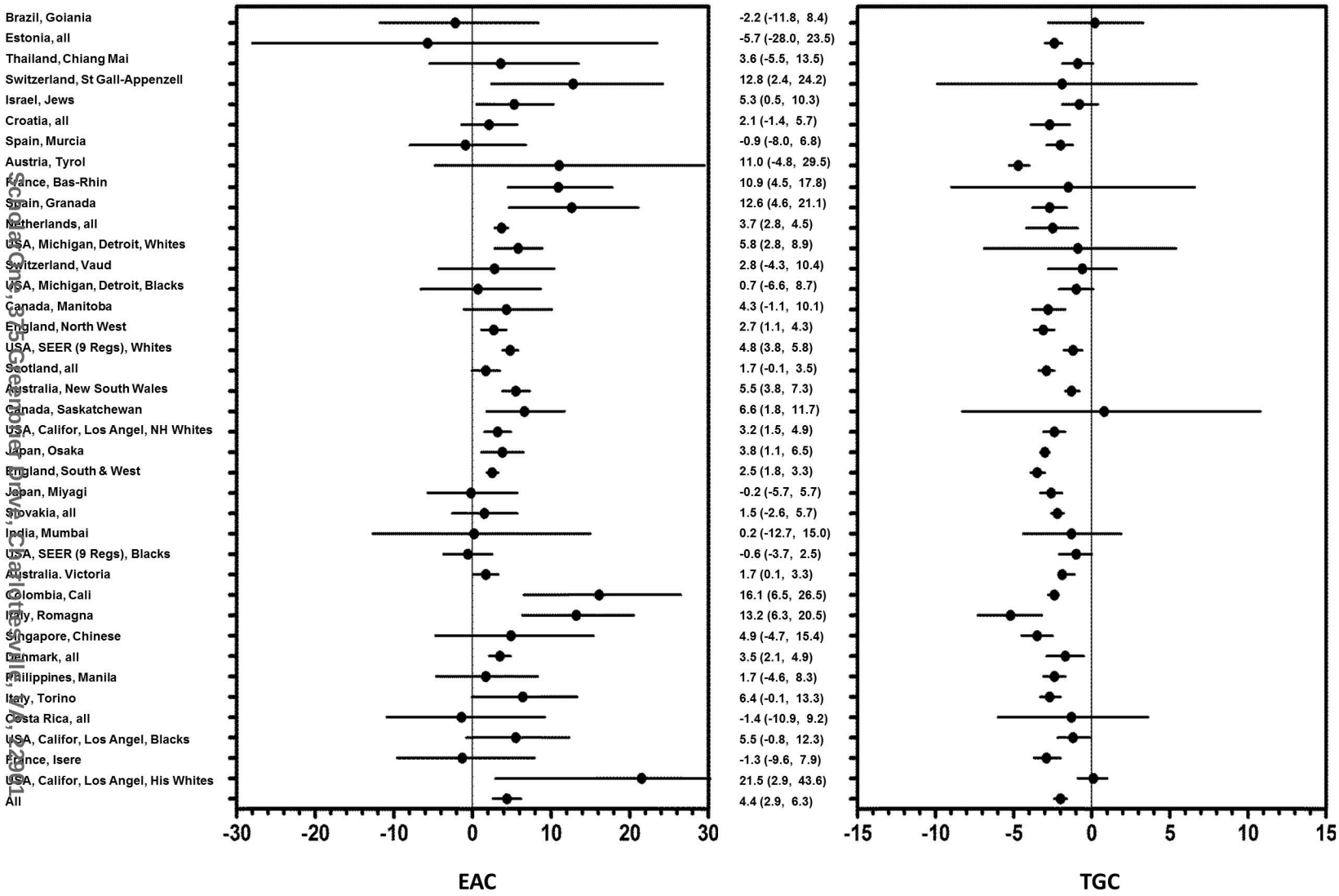

Fig Suppl. 3

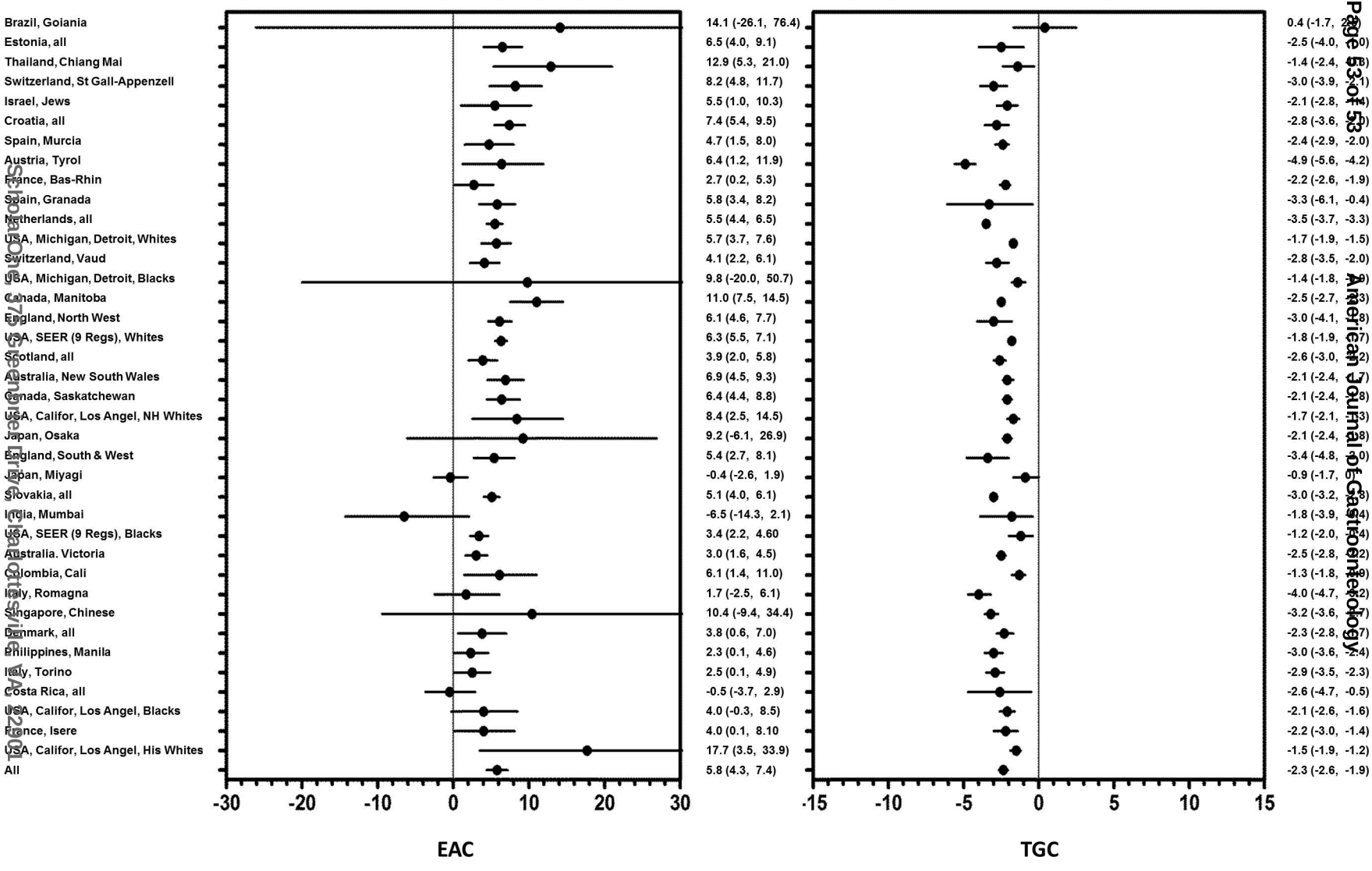

Fig Suppl. 4